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Pathology

786. **Application of the Fluorescent Antibody Technique to the Study of the Pathogenesis of Nephritis in Man.** (La tecnica degli anticorpi fluorescenti applicata allo studio della patogenesi della nefrite umana)

B. C. SEEGAL, K. C. HSU, E. FIASCHI, and G. ANDRES. *Rassegna di fisiopatologia clinica e terapeutica [Rass. Fisiopat. clin. ter.]* 31, 523-536, June [received Sept.], 1959. 3 figs., 9 refs.

At Columbia University, New York, and the Institute of Special Pathology, Rome, serial sections of needle biopsy specimens of the kidney from 2 healthy subjects, one patient with pyelonephritis, and 22 with acute, subacute, or chronic nephritis were placed in contact with anti-human globulin, anti-human gamma globulin, and antistreptococcal (Group A, Type 12) sera prepared by rabbit immunization and labelled with fluorescent material. The presence of absorbed sera on the sections was shown by green-yellow fluorescence on microscopical examination under ultraviolet light.

A positive result was obtained in 15 of 17 biopsy specimens marked with anti-human globulin, in 9 of 15 cases marked with anti-human gamma globulin, and in 5 of the 22 cases of nephritis marked with antistreptococcal serum. Of these last 5 cases, 4 also gave a positive result with anti-human gamma globulin and 3 showed a raised antistreptolysin-O titre. The only positive reaction in the specimens from normal subjects was to anti-human globulin in one case. It was noted that the fluorescence was mainly located in the glomeruli and the authors suggest that nephritis may be due to an antigen-antibody reaction in the glomeruli. It is stressed that these are preliminary results which are, of necessity, tentative, but the authors consider that the fluorescent antibody technique provides a valuable research tool.

H. Caplan

787. **Value of the Plasma Clotting Time in Siliconized Tubes in the Surveillance of Anticoagulant Therapy in Cardiology.** (Intérêt du temps de coagulation plasmatique en tubes siliconés dans la surveillance du traitement anticoagulant en cardiologie)

M. MOUQUIN, R. SAUVAN, J. RICHON, M. SAMAMA, and M. HODARA. *Presse médicale [Presse méd.]* 67, 1629-1630, Sept. 26, 1959. 3 figs., 1 ref.

The authors describe a method for the determination of the plasma coagulation time in siliconized glass tubes, as follows. Of a small quantity of blood withdrawn by venepuncture the first 2 or 3 ml. is discarded and the next 4 ml. collected in a tube containing 1 ml. of 4% sodium

citrate solution. As soon as possible after mixing the tube is put in a refrigerator at 4° C. The test, which is carried out in duplicate, should be performed within 4 hours by the following technique: 0.5 ml. of plasma is transferred to a tube in a water bath at 37° C. for 5 to 6 minutes, 0.1 ml. of warmed 1.29% solution of calcium chloride is then added, and the time taken for coagulation to occur is noted. The normal range is from 5 minutes, 30 seconds to 8 minutes, 10 seconds (mean time 7 minutes). The test has been used to observe the results of anticoagulant therapy in 34 cases followed up for periods of 15 days to 2½ months. At the same time Quick's test was performed, the coagulation time (by Howell's method) and heparin clotting time determined, and thrombo-elastography carried out in every case. The authors claim that the plasma coagulation time in siliconized tubes is an accurate, sensitive, and simple technique for use in conjunction with Quick's test in cases undergoing anticoagulant therapy.

A. W. H. Foxell

788. **The Value of the Examination of the Cerebrospinal Fluid in the Diagnosis of Intracranial Tumours**

W. H. McMENEY and J. N. CUMINGS. *Journal of Clinical Pathology [J. clin. Path.]* 12, 400-411, Sept., 1959. 11 figs., 35 refs.

The authors describe the results of examination of the cerebrospinal fluid (C.S.F.) in 916 cases of histologically verified intracranial tumour seen at the National Hospital, Queen Square, and Maida Vale Hospital, London, over a 20-year period. The detailed results are tabulated. In all recent cases films prepared from a centrifuged deposit of the C.S.F. have been examined after staining by Leishman's method, which the authors find more satisfactory than that of Papanicolaou for this purpose.

The protein content of the C.S.F. was raised above 100 mg. per 100 ml. in about one-third of the cases and above 200 mg. per 100 ml. in about 10%; however, in all of the 50 cases of acoustic neuroma the level was uniformly high. Pleocytosis was most commonly found in cases of cerebral glioma (20.4% of 172 cases), but on a percentage basis was equally common in secondary carcinoma of the brain (20.4% of 59 cases). A raised cell count in the C.S.F. is considered to be of serious import, since it suggests that the tumour is in contact with the ventricles. If in addition the fluid is tinged yellow "necrosis or haemorrhage should be suspected and this is usually indicative of malignancy". The cells present are usually neutrophil granulocytes, lymphocytes,

and histiocytes, the presence of the last two types often indicating that necrosis of the tumour has occurred, while a lymphocytosis indicates a reaction of the ependyma or pia-arachnoid. The authors review the 21 previously reported cases in which tumour cells were found in the C.S.F. of patients with primary intracerebral tumour and refer to the much more frequent finding of carcinoma cells in the C.S.F. of patients with secondary intracranial tumours. In the present series tumour cells were found in 17 cases by the help of the newer technique referred to, although such identification often presents considerable difficulties, which are discussed. Short histories of 13 of these cases, which included cases of pituitary adenoma, oligodendroglioma, chordoma, and meningioma, are presented. A falling glucose level in the C.S.F. is thought to be highly suggestive of carcinomatous meningitis, and it is noted that a cell count which is within normal limits does not exclude this diagnosis.

R. Wyburn-Mason

CHEMICAL PATHOLOGY

789. Mucoproteins of Cerebrospinal Fluid and Blood in Neurologic Disorders

A. ZLOTNICK, E. WEISENBERG, and I. CHOWERS. *Journal of Laboratory and Clinical Medicine [J. Lab. clin. Med.]* 54, 207-212, Aug., 1959. 15 refs.

The mucoprotein levels in blood and cerebrospinal fluid (C.S.F.) were determined in 49 patients suffering from various neurological disorders and in 8 controls at Rothschild Hadassah University Hospital, Jerusalem. It was found that the mucoprotein content of the C.S.F. increased in infections (by a mean value of 14.3%) and in the presence of tumours of the central nervous system (by a mean value of 13.2%). No direct correlation could be demonstrated between the mucoprotein level in the serum and that in the C.S.F., nor could any correlation be found between the total protein content and the mucoprotein content of the C.S.F.

These findings suggest that the presence of a tumour of the central nervous system should be suspected in those cases in which the mucoprotein level in the C.S.F. is high and an acute infection or abscess of the central nervous system can be ruled out. The authors consider that if these results are confirmed in further studies on many more patients the determination of the mucoprotein content of the C.S.F. may become an important diagnostic aid in cases of tumour of the central nervous system.

L. A. Elson

790. "Myeloma" Serum Electrophoretic Patterns in Conditions Other than Myelomatosis

J. A. OWEN, W. R. PITNEY, and J. F. O'DEA. *Journal of Clinical Pathology [J. clin. Path.]* 12, 344-350, July [received Sept.], 1959. 2 figs., 45 refs.

Ten patients are described in whom the serum electrophoretic pattern was of the myeloma type but in whom a diagnosis of myelomatosis was not established. In 4 patients the abnormal protein was a macroglobulin. In 5 patients there was evidence of reticulo-endothelial disease whilst one patient suffered from a carcinoma of

the thyroid gland. In the other patients there was no evidence of neoplasia. Four patients showed an increased susceptibility to infection which was possibly related to hypo- γ -globulinaemia.

It is concluded that whilst discrete abnormal electrophoretic components in serum are most often associated with myelomatosis or lymphoma, they are occasionally present in a variety of other conditions.—[Authors' summary.]

791. Plasma Creatinine Level and Creatinine Clearance as Tests of Renal Function

K. D. G. EDWARDS and H. M. WHYTE. *Australasian Annals of Medicine [Aust. Ann. Med.]* 8, 218-224, Aug. [received Oct.], 1959. 4 figs., 23 refs.

Determination of creatinine clearance after administration of exogenous creatinine as a measure of the glomerular filtration rate has been described as "inaccurate and misleading". Working at the Kanematsu Research Institute, Sydney, the authors have measured plasma creatinine levels by separating the true creatinine from other chromogens by adsorption on to fuller's earth, with subsequent elution of creatinine and development of colour with alkaline picrate; protein precipitation, pH, and temperature are controlled as previously described (*Aust. J. exp. Biol.*, 1958, 36, 383).

They show that in normal subjects plasma creatinine levels were 0.93 ± 0.14 mg. per 100 ml. for males and 0.73 ± 0.14 mg. per 100 ml. for females; and that the endogenous creatinine clearance rate was 108 ± 16 ml. per minute for normal males and 104 ± 14 ml. per minute for normal females, corrected for a surface area of 1.73 sq. metre. They also showed that there was a good correlation between the plasma creatinine level, endogenous creatinine clearance corrected for surface area, and renal urea clearance rate, but that the correlation was less close with the blood urea nitrogen content. They therefore conclude that the plasma creatinine concentration as measured by the method described is a better index of renal function than the blood urea concentration.

K. G. Lowe

792. Tests for Phenylketonuria: Results of a One-year Programme for Its Detection in Infancy and among Mental Defectives

N. K. GIBBS and L. I. WOOLF. *British Medical Journal [Brit. med. J.]* 2, 532-535, Sept. 26, 1959. 22 refs.

Early detection and treatment of phenylketonuria are essential if irreversible mental deterioration is to be avoided. A scheme which aimed at the early detection of cases of phenylketonuria was tried in Cardiff, mothers of infants born in the city over the 12-month period March 1, 1958, to March 1, 1959, being asked to provide a fresh specimen of the infant's urine when the child was 3 weeks old.

Although there were 4,530 live births in Cardiff during the year, only 1,192 urine specimens were obtained. All were tested with ferric chloride and many of them also with "phenistix", a test strip which, when dipped in urine, turns green in the presence of phenylpyruvic acid. Of the 1,192 specimens, 51 were strongly alkaline and were

rejected; of the remaining 1,141 specimens, one gave a positive reaction for phenylpyruvic acid.

The problems of such mass schemes for the early detection of phenylketonuria are discussed. It is suggested that the use of phenistix provides a simpler, quicker, and more specific method of testing urine than any hitherto employed. *H. Harris*

793. Excretion of Acid Mucopolysaccharides in the Urine of Patients with Malignant Neoplastic Diseases

C. RICH and W. P. L. MYERS. *Journal of Laboratory and Clinical Medicine* [J. Lab. clin. Med.] 54, 223-228, Aug., 1959. 15 refs.

Urinary excretion of acid mucopolysaccharides was studied in 29 patients at the James Ewing Hospital, New York, suffering from disseminated malignant neoplastic diseases, the method of Di Ferrante and Rich (J. Lab. clin. Med., 1956, 48, 491) being used. Of 13 patients with carcinoma, excretion was normal in 6 and increased in 7. In 8 out of 9 patients with leukaemia and in all 7 with multiple myeloma or sarcoma there was increased excretion of mucopolysaccharides. No significant difference was observed on chemical analysis of the mucopolysaccharides between the urine of patients with carcinoma or leukaemia and the urine of healthy subjects.

L. A. Elson

794. Gastric Proteolysis in Disease. II. The Proteolytic Activity of Gastric Juice and Gastric Mucosal Extracts from Patients with Chronic Gastric and Duodenal Ulcer

W. H. TAYLOR. *Journal of Clinical Pathology* [J. clin. Path.] 12, 338-343, July [received Sept.], 1959. 2 figs., 19 refs.

The author has studied the pH activity curves for the digestion of protein by gastric juice and by extracts of the gastric mucosa from 22 patients with duodenal ulcer and 3 with gastric ulcer. In previous investigations on normal subjects the pH activity curve for the digestion of egg albumen by gastric juice showed one maximum below pH 5 (pH 1.5 to 1.8) in 5 cases and 2 maxima (pH 1.5 to 1.6 and 2.5 to 2.8) in a further 2 cases. For the digestion of other proteins (plasma protein, serum albumin, and bovine plasma albumin) there were 2 maxima below pH 5 (pH 1.7 to 2.4 and 3.3 to 4.0) in 17 normal subjects.

The gastric juice of 3 patients with peptic ulcer digested egg albumen with 2 maxima below pH 5 (pH 1.5 to 1.6 and 2.6 to 3.1). The gastric juice of 7 of 11 patients digested other proteins with three maxima below pH 5 (pH 1.5 to 2.1, 2.5 to 3.1, and 3.8), the activity curves in the remaining 4 cases being normal. Whole and fundic mucosal extracts from 12 of 16 patients digested proteins other than egg albumen with 3 maxima below pH 5 (pH 1.5 to 2.2, 2.5 to 3.2, and 3.3 to 3.9). The fundic extracts of 2 patients digested egg albumen with maxima at pH 1.5 to 1.7 and 2.5 to 3.1. Pyloric mucosal extracts of 3 of 9 patients digested plasma proteins with three maxima (at pH 1.7 to 1.9, 2.5 to 2.8, and 3.3 to 3.8) but in the remaining 6 cases normal curves were obtained with maxima at pH 1.7 to 2.1 and 2.8 to 3.4.

The gastric juice of 2 patients with peptic ulcer and the fundic mucosal extract of a third hydrolysed the specific pepsin substrate benzyl oxycarbonyl-L-glutamyl-L-tyrosine with a single maximum at pH 3.6 to 4.0, the activity curve resembling that of normal subjects. Proteinase activity was present over the pH range 6.4 to 7.4 in 3 of 6 extracts of fundic mucosa and in 3 of 5 extracts of pyloric mucosa from patients with peptic ulcer. Two of these extracts showed a maximum at pH 7.2.

The author did not succeed in separating individual enzymes responsible for the pH maxima by salt fractionation. He discusses various hypotheses which might account for the occurrence of pH activity curves with 3 maxima and concludes that the available evidence favours the formation and secretion of an abnormal enzyme or enzymes by the mucous membrane in such cases. He suggests that peptic ulceration may occur more readily in those subjects whose gastric juice digests proteins with three maxima than in the remainder of the population.

Victor M. Rosenoer

MORBID ANATOMY AND CYTOLOGY

795. Development of Cerebral Atherosclerosis in Various Age Groups

J. MOOSSY. *Neurology* [Neurology (Minneapolis)] 9, 569-574, Sept., 1959. 4 figs., 12 refs.

The development and morphology of the lesions of cerebral atherosclerosis in various age groups were studied in the intracranial portions of the internal carotid and vertebral arterial systems removed at necropsy in 122 unselected cases at the Charity Hospital of Louisiana, New Orleans. The arteries were dissected from the fresh brain, opened longitudinally, and flattened on cardboard, the intimal surfaces being exposed. After fixation in 10% formalin the vessels were stained with Sudan IV. The intimal surfaces were studied with the naked eye and with the aid of a dissecting microscope. The total intimal surface available for examination was measured in square millimetres, as was the amount of intimal surface stained red. Specimens representative of each decade of life were subsequently sectioned for microscopy. Atherosclerosis of cerebral vessels appears in the third decade of life and is usually preceded by changes in the aorta and coronary arteries.

Hugh Garland

796. Brain Changes in Ruptured Intracranial Aneurysm

B. E. TOMLINSON. *Journal of Clinical Pathology* [J. clin. Path.] 12, 391-399, Sept., 1959. 6 figs., 20 refs.

The changes in the brain in ruptured intracranial aneurysm were studied in a series of 32 consecutive fatal cases seen at the Newcastle General Hospital, particular attention being paid to the occurrence of ischaemic lesions and of localized subarachnoid haematomata. In addition to intracranial haemorrhage ischaemic lesions were very common, and massive infarction was present in 13 of the 32 cases. The author considers that ischaemic lesions probably cause most of the residual disabilities in the non-fatal cases of subarachnoid haemorrhage.

morrrhage. In 4 cases in the series degeneration of the granular layer of the cerebellum was present in varying degree and appeared to be a terminal event. It is pointed out that blood tends to collect between the frontal lobes, in the Sylvian fissure, and in the depths of the sulci and in these positions may form large haematomata which may cause death by acting as space-occupying lesions and may lead to intracerebral and intraventricular haemorrhage. These lesions are probably important in the development of infarction, and the mechanism by which this could occur is discussed. The author states that surgical treatment of the aneurysm within a few hours of haemorrhage often has "dire results . . . but the knowledge that these large collections are usually in or between the frontal lobes, or in the Sylvian fissure or temporal lobes, should make attempted evacuation a reasonable possibility in patients otherwise considered hopeless".

R. Wyburn-Mason

797. Morphological Aspects of the Pathology of the Pulmonary Circulation. (Apports morphologiques de la pathologie de la circulation pulmonaire)

H. MEESSEN. *Acta cardiologica* [*Acta cardiol. (Brux.)*] 14, 211-242, 1959. 19 figs., bibliography.

Writing from the Düsseldorf Academy of Medicine, the author first discusses the normal post-mortem pulmonary angiogram. The pulmonary artery and vein give distinctive pictures, but the bronchial arteries, because of numerous anastomoses, are more difficult to demonstrate.

He then describes the vascular changes in the lungs in various pathological conditions as seen in necropsy and operation specimens examined angiographically. Anastomoses between the pulmonary artery and vein are commonly aneurysmal arterio-venous fistulae and form part of the Rendu-Osler-Weber syndrome. Since 1951 the author has seen 7 such cases which are not reported here, but 4 other cases are briefly described and illustrated. In one of these a single arterio-venous aneurysm was present and in another an aneurysm was demonstrated both in the left and in the right lung, together with patent ductus arteriosus. In the third case no aneurysm was present, but arterio-venous communication was established by unusually large channels resembling capillaries—possibly a new form of vascular disease. The fourth case was one of communication between the right pulmonary artery and a saccular aneurysm of the left auricular appendage. In 2 cases of arterio-arterial communication seen since 1949 there was an incomplete truncus arteriosus with communication between the aorta and pulmonary artery. Among numerous cases of patent ductus arteriosus was one showing dilatation of the pulmonary artery with closely set, slightly spirally twisted tufts of branches and numerous anastomoses with the bronchial arteries. In a case of tight mitral stenosis injection of the pulmonary artery filled the bronchial arteries and the aorta. An impressive number of pulmonary arterial branches was seen in a case of emphysema. In specimens of bronchiectatic lung obtained at lobectomy the thickened bronchial wall and the fibrous, scarred parenchyma are so densely vascularized

that distinction between branches of the pulmonary and bronchial arteries often becomes impossible. A composite diagram is given showing the anastomoses found in 108 cases of Fallot's tetralogy and related malformations, irrefutable evidence being obtained of short-circuits between the aorta and the pulmonary artery.

The second part of the paper describes an experimental electron-microscopical study of the changes occurring in the cells of the pulmonary alveolar epithelium, and particularly in their mitochondria, as a result of changes in the composition of the inhaled air. Lowering of the oxygen tension to a level corresponding to a height of 10,000 metres above sea level for 1½ hours produces marked but reversible swelling of the alveolar mitochondria in rats; longer exposure to this degree of hypoxia leads to death of the cells. Respiration of pure oxygen under normal pressure for 8 hours produces vacuolation and vesiculation of the mitochondria. Exposure to 3.5% carbon dioxide produces a striking lamelliform transformation of the mitochondria which is characteristic of the action of CO₂ and is particularly well marked in the foetal rat. Intraperitoneal administration of the carbonic anhydrase inhibitor "diamox" (acetazolamide) prevents the development of this change for 2 to 6 hours. The lamelliform response to exposure to CO₂ appears to be especially important because the respiratory epithelium, more than any other tissue in the body, is exposed to CO₂. These findings are discussed and their physiological basis in relation to regulation of the pulmonary capillary circulation critically examined.

F. Hillman

798. The Exudative Lesion in Diabetic Glomerulosclerosis

A. LAUFER and O. STEIN. *American Journal of Clinical Pathology* [*Amer. J. clin. Path.*] 32, 56-61, July, 1959. 4 figs., 15 refs.

The pathogenesis of the exudative renal lesion in diabetic glomerulosclerosis and the relationship of this lesion to arteriosclerosis with and without diabetes were studied at Hadassah University Hospital, Jerusalem, in material obtained at necropsy on 18 unselected diabetic patients and 47 non-diabetic patients with arteriosclerotic changes in the kidneys. The presence or absence of shock and of adrenal hyperplasia before death was noted, since it was considered that vascular shock might cause increased vascular permeability, while a raised secretion of adrenal steroids might produce increased vascular fragility. It was found that in arteriosclerotic kidneys there was a definite increase in the incidence of exudative renal lesions if diabetes was present. The severity of the lesions was also related to the degree of arteriosclerosis and adrenal cortical hyperplasia. Shock occurred in the terminal stages of the disease in a large proportion of diabetic patients who manifested exudative glomerulosclerosis, but it was noted only in a minority of non-diabetic patients with this lesion.

The authors suggest that the arteriolar changes need not be regarded as the sole cause of the exudative lesion, which appears most often in diabetics and also when other factors associated with increased permeability of

the vessels are present; the increased secretion of adrenal cortical steroids may be a common factor in the production of the exudative lesion.

J. B. Wilson

799. Resolution of Glomerular Lesions in the Nephrotic Syndrome Treated with Cortisone: Electron Microscopic Studies in an Adult Case

M. K. MACDONALD, A. T. LAMBIE, and J. S. ROBSON. *Scottish Medical Journal* [Scot. med. J.] 4, 415-421, Sept., 1959. 6 figs., 7 refs.

Kidney biopsy specimens from a patient with the nephrotic syndrome were examined before and after treatment with cortisone by both light and electron microscopy, and the findings are reported in this paper from the University of Edinburgh. The abnormalities described were observed only by electron microscopy. Before administration of cortisone examination of the glomerular tuft revealed marked blunting of the pedicles of the epithelial cells, but after nine months' treatment with cortisone there was complete resolution of the pedicular abnormalities with clinical recovery. No changes were noted at any time in the basement membrane.

The authors review the literature and suggest that the abnormality described is probably the primary lesion and that thickening of the basement membrane follows this. The degree of thickening of the basement membrane may be the factor which determines whether or not recovery is possible.

J. B. Wilson

800. The Membranous and Proliferative Glomerulonephritis of Hepatic Cirrhosis

E. R. FISHER and H. R. HELLSTROM. *American Journal of Clinical Pathology* [Amer. J. clin. Path.] 32, 48-55, July, 1959. 6 figs., 18 refs.

A number of renal lesions have been observed in association with cirrhosis of the liver. In this paper from the University of Pittsburgh, Pennsylvania, a distinctive but not specific glomerular lesion is described which was found at necropsy in 25 out of 100 consecutive cases of Laennec's cirrhosis. The lesion was characterized by a diffuse or focal fibrillary thickening of the endothelial stalk, which in some instances also involved portions of the basement membrane of glomerular capillaries. In addition the glomeruli exhibiting this lesion were more cellular than normal. No relationship was found between these lesions and other clinical and pathological features.

J. B. Wilson

801. Tay-Sachs' Disease with Visceral Involvement and Its Relationship to Niemann-Pick's Disease

R. M. NORMAN, H. URICH, A. H. TINGEY, and R. A. GOODBODY. *Journal of Pathology and Bacteriology* [J. Path. Bact.] 78, 409-421, 1959. 16 figs., 16 refs.

The post-mortem findings in a case of Tay-Sachs disease with exceptionally severe visceral involvement are described and discussed in relation to similar findings in a case of Niemann-Pick disease. Both cases were seen at Frenchay Hospital, Bristol, the patients being, respectively, a male aged 17 months and a female aged 15½ months. Paraffin and frozen sections were examined microscopically after staining by conventional methods

and a number of organs were subjected to chemical analysis. In both cases there were widespread degenerative cellular changes in the viscera with an accompanying infiltration of foamy histiocytes. The brain in the case of Tay-Sachs disease, however, contained a large amount of ganglioside, while the liver contained a large excess of hexosamine. In the case of Niemann-Pick disease sphingomyelin was stored in the brain, liver, and spleen; other features which distinguished it from Tay-Sachs disease were more pronounced haematoxylinophilic staining and very feeble or negative staining of parenchymal and foam cells by the periodic-acid-Schiff method.

A. Wynn Williams

802. Lipoblastic Tumors of Children

S. L. KAUFFMAN and A. P. STOUT. *Cancer* [Cancer (Philad.)] 12, 912-925, Sept.-Oct., 1959. 12 figs., bibliography.

In this paper from Columbia University College of Physicians and Surgeons and the Francis Delafield Hospital, New York, (the first of a series planned to deal with tumours of mesenchymal origin in childhood) are discussed only those tumours considered to be of pure lipoblastic origin, each section consisting of a review of the literature illustrated by material from the personal files of the senior author (Stout).

After considering the lipomata and 2 cases of hibernoma [a part of the paper chiefly of interest because of the useful summary of the literature it contains], the authors briefly discuss their 4 cases of lipoblastomatosis—a benign, circumscribed, lobulated tumour of embryonal lipoblasts which may expand into, but does not infiltrate, adjacent tissues. All 4 cases occurred in infants aged under one year. Incomplete removal, unavoidable in one of these cases, was not necessarily followed by recurrence, at least not during a follow-up of 2½ years.

The major part of the paper deals with a group of tumours which the authors regard as liposarcomata, but which have been given a variety of names by other authors; they accept only 15 cases from the literature and describe 13 of their own. This tumour, which may appear at any age throughout childhood, but more frequently at the two extremes of the age range, is infiltrative rather than nodular and recurs locally if inadequately excised, but rarely metastasizes. Macroscopically, it resembles the lipoma and usually arises in fascial planes. Histologically, 9 of the authors' 13 cases were well differentiated, consisting of foci of lipoblasts with a mesh of capillaries in a myxomatous stroma, but without the smooth muscle or angiomatous tissue of the mesenchymoma. In 2 of the remaining cases, otherwise falling within this group, variation in the character of the lipoblasts was more prominent and cellularity greater. The last 2 tumours in this group were poorly differentiated and devoid of the characteristic stroma and vascular pattern, while the lipoblasts were bizarre and frequently multinucleated. Treatment in all cases was by local excision. Follow-up information on these cases has been imperfect, but so far as was ascertainable local recurrence has taken place in only 2 cases and there was no instance of distant metastasis.

E. G. Hall

Microbiology and Parasitology

803. Correlation between *in vitro* Studies and Response to Antibiotic Therapy in Staphylococcal Bacteremia

F. M. ABBoud and B. A. WAISBREN. *A.M.A. Archives of Internal Medicine* [A.M.A. Arch. intern. Med.] 104, 226-233, Aug., 1959. 7 figs., 23 refs.

The selection of the best antibiotic for the treatment of staphylococcal bacteraemia is of major importance. As a contribution to this problem the authors have studied, at Marquette University School of Medicine, Milwaukee, Wisconsin, the results of treatment with antibiotics in the records of 100 consecutive cases of bacteraemia due to *Staphylococcus aureus* during a 5-year period, and have compared them with the reported sensitivity of the organism as determined by the tube-dilution method.

Of 81 patients given penicillin at some time during their illness, 57 showed no clinical response, 18 responded, and in 6 the response was "undetermined", that is, the evidence was insufficient to allow of classification. In all 18 responding cases the organism was sensitive *in vitro* to a concentration of 3 μ g. of penicillin per ml. or less, but no case responded when the minimum inhibitory concentration (M.I.C.) was above this level. However, even when the organism appeared to be sensitive to the antibiotic at this level there was not necessarily a clinical response in all cases. Chloramphenicol was used in 53 cases, but produced a response in only 4. The M.I.C. in this group was among the lowest in the series, but nevertheless it is concluded that chloramphenicol was a relatively ineffective drug in this series of cases. Erythromycin was given to 43 patients with a resulting response in 14, no response in 23, and an undetermined response in 6. In 18 cases the M.I.C. was 6 μ g. per ml. or higher and none of these patients responded, while of 25 cases with an M.I.C. of 3 μ g. per ml. or less, only 7 did not respond. Streptomycin was given in 22 cases, with a clinical response in only 3, in which the M.I.C. was 6 μ g. per ml. or lower; in 3 cases the response was undetermined and in the remaining 16 the M.I.C. was 6 μ g. per ml. and there was no clinical response. Tetracycline, used in the treatment of 41 patients, produced a clinical response in 15 cases, in all of which the organism was sensitive to 6 μ g. per ml. or less; in 17 cases in which the staphylococcus was resistant at that level there was no clinical response, but on the other hand 4 cases did not respond clinically although the M.I.C. was low. Similar results were obtained in a few cases treated with vancomycin, novobiocin, and neomycin.

Probably the most important finding emerging from this study was the distinct correlation between the resistance as demonstrated *in vitro* and lack of clinical response when an M.I.C. of 6 μ g. per ml. was taken as the dividing line; on this basis, in only one instance out of 133 trials was a clinical response obtained when the staphylococcus was sensitive only to concentrations above 6 μ g. per ml.

The authors therefore suggest that as an alternative method of laboratory testing a single tube containing 6 μ g. of antibiotic per ml. could be used, and indeed they have now adopted this technique at Milwaukee County Hospital; details of their method are given. In the case of penicillin no response was obtained in cases in which the organism was resistant at an M.I.C. level over 3 μ g. per ml., despite the use of up to 60,000,000 units of penicillin per day. On the other hand a clinical response was frequently obtained at sensitivity levels of 1.5 and 3 μ g. per ml. (0.9 to 1.8 units). Although staphylococci that are resistant to more than one unit of penicillin inevitably produce penicillinase, the present findings appear to suggest nevertheless that the production of penicillinase by a strain of staphylococcus does not necessarily make such a strain clinically resistant to the action of penicillin.

R. F. Jennison

SEROLOGY AND IMMUNOLOGY

804. The Indirect Haemagglutination Test in Dysentery Caused by *Shigella sonnei* and *Shigella flexneri*

J. HAVLÍK, B. KOTT, and V. POTUŽNÍK. *Journal of Clinical Pathology* [J. clin. Path.] 12, 440-443, Sept., 1959. 12 refs.

It often happens that no bacteriological diagnosis can be made in patients suffering from enteric infections, particularly if, as is often the case nowadays, they have been treated with antibiotics. In this investigation of the indirect haemagglutination test in the diagnosis of dysentery, reported from the Faculty of Hygiene, Prague, 689 sera from a wide variety of patients, ranging from cases of typical acute dysentery to the symptomless carrier, were examined. *Shigella sonnei* or *Sh. flexneri* were isolated in each case. Antigens were prepared from both smooth and rough phases of *Sh. sonnei* and a mixed culture of *Sh. flexneri*—details of the preparation of these antigens are given—and the bacterial antigen suspensions were absorbed on to human Group-O, Rh-negative erythrocytes. The test consisted in mixing the patient's inactivated serum with a 1% suspension of modified erythrocytes, this mixed suspension being then centrifuged for 2 minutes at 800 r.p.m. and examined for agglutination. In some preliminary experiments the modified erythrocytes were tested for specificity against hyperimmune rabbit serum prepared against various members of the Genus *Enterobacteriaceae* and were shown to be highly specific; very few of the other antigens produced a positive result, and then very weakly, whereas with the various strains of *Shigella* strongly positive results were obtained. There was no cross-reaction between antibodies to *Sh. sonnei* and those to *Sh. flexneri*. Further tests by the haemagglutination technique of 50 samples of blood taken from the umbilical vein of newborn infants all gave negative reactions. Neither the

duration nor speed of centrifugation seemed to influence the result of the reaction.

Of the 689 samples of serum examined, 620 were from 210 patients suffering from Sonne dysentery and 69 from 32 patients with Flexner infection. A titre of 1:50 was considered to be highly suggestive of infection, while a titre of 1:100 or higher was accepted as a positive result, a rise in antibody being very significant. Suggestive titres usually appeared at the end of the first week after the onset of symptoms and remained positive for several weeks. Most sera showed a positive or at least a suggestive result in the first specimen. A few patients gave reactions to both types of *Shigella*, probably as a result of previous infection with the other type. The sera from 12 cases of each of the two types of dysentery were examined by both the haemagglutination and the Widal techniques. It was noted that with the Widal technique the agglutination titres were either negative or low, and always lower than the titres obtained by the haemagglutination test.

The authors conclude that the haemagglutination procedure is highly specific and more sensitive than the agglutination technique and should be used in the diagnosis of bacillary dysentery—but not, of course, to the exclusion of cultural techniques. They add that the haemagglutination technique is particularly useful as a proof of the disease in patients undergoing treatment with antibiotics, in whom culture of the faeces is often negative.

R. F. Jennison

805. Serological Identification of *Shigella flexneri* by Means of Fluorescent Antibody

E. H. LABREC, S. B. FORMAL, and H. SCHNEIDER. *Journal of Bacteriology* [J. Bact.] 78, 384–391, Sept., 1959. 3 figs., 13 refs.

By current methods and with the best facilities the identification of the aetiological agents of enteric disease requires a minimum of 24 to 72 hours. In the present study, carried out at the Walter Reed Army Institute of Research, Washington, D.C., strains of *Shigella flexneri* were typed by the fluorescent antibody technique and by slide agglutination and the specificity of the two methods compared. Fluorescent antibody was made by conjugating fluorescein isocyanate or isothiocyanate with globulin from rabbit antisera. Smears were made from pure cultures on nutrient agar plates, fixed with alcohol, and stained with the fluorescein-labelled globulin which had been diluted as far as possible without losing its staining ability. With the polyvalent grouping sera significant staining of *Sh. flexneri* occurred only with Group-B antisera, and the strains were then typed satisfactorily with labelled, adsorbed, type-specific antisera. There was a good correlation with the results of slide agglutination tests.

In the second part of this study attempts to identify *Sh. flexneri* in the faeces of infected guinea-pigs were not so successful. The sera had been adsorbed with normal guinea-pig antigens, but non-specific results were still obtained. Some non-lactose fermenting organisms, which were also present in the faeces of healthy human beings, showed fluorescence, presumably because they

shared a common antigen with *Sh. flexneri*. Other organisms fluoresced non-specifically because they reacted with "normal" antibodies contained in the labelled globulin. These difficulties were not overcome. The indirect staining method was not satisfactory either, because the available sheep anti-rabbit globulin also contained normal antibody to several organisms as well as to various strains of *Shigella*. Janice Taverne

806. Enzyme-treated Red Blood Cells of Sheep in the Test for Infectious Mononucleosis

L. H. MUSCHEL and D. R. PIPER. *American Journal of Clinical Pathology* [Amer. J. clin. Path.] 32, 240–244, Sept., 1959. 10 refs.

The test described in this paper from the Walter Reed Army Institute of Research, Washington, D.C., is based on the observation of Wöllner (*Z. Immun.-Forsch.*, 1955, 112, 290) that sheep erythrocytes treated with papain do not react with the heterophile antibody of infectious mononucleosis.

For the test inactivated serum is used, with and without previous absorption against enzyme-treated sheep erythrocytes, doubling dilutions of absorbed and of unabsorbed serum being tested against both untreated and treated sheep erythrocytes. The methods used are simple and are adequately described in the paper [to which reference should be made for the details]. In 13 well-documented cases of infectious mononucleosis the enzyme-treated erythrocytes gave a significantly lower titre against unabsorbed serum than untreated cells, enzyme treatment having inactivated the receptor for the heterophile antibody. With absorbed sera the titre against untreated erythrocytes was the same in each case as with unabsorbed serum, but treated cells gave no agglutination even at the first dilution (1:7), this being used as a check on the completeness of absorption of the serum. The same sera were tested in parallel in the usual way after guinea-pig and beef erythrocyte absorption, the results also being compatible with the diagnosis of infectious mononucleosis, although in 12 cases the titre fell to one-fourth of its original value after absorption with guinea-pig kidney.

In conditions other than infectious mononucleosis unabsorbed serum gives a higher titre against enzyme-treated cells than against untreated cells, and absorbed serum agglutinates neither treated nor untreated cells; in both these respects the reaction is in the opposite direction to that obtained in infectious mononucleosis, which renders the test more specific. Normal sera only exceptionally give any reaction, and the titres reached are very low.

As patients with infectious mononucleosis sometimes develop antibodies against Sendai virus, rabbits were sensitized with Sendai virus and their sera used for the test. It was clearly demonstrated that the antibody to Sendai virus reacts differently from that to infectious mononucleosis. It is pointed out that although the standard differential absorption tests are usually adequate to distinguish the agglutinins of infectious mononucleosis from sheep-cell agglutinins arising from other sources, absorption with guinea-pig kidney (a source of Forssman

antigen) often reduces the agglutination titre of serum from cases of infectious mononucleosis despite the fact that the heterophile antibody is not of the Forssman type, and this may occasionally lead to incorrect interpretation of the agglutination test. On the other hand absorption with enzyme-treated cells never reduces the agglutination titre of the serum, treatment with papain completely destroying the reactivity of the erythrocytes with infectious mononucleosis antibody. The unequivocal nature of the results obtained thus makes the new test a valuable diagnostic procedure. *F. Hillman*

807. Biologic Activity of Soluble Antigen-Antibody Complexes. V. Change of Optical Rotation by the Formation of Skin Reactive Complexes

K. ISHIZAKA and D. H. CAMPBELL. *Journal of Immunology* [J. Immunol.] 83, 318-326, Sept., 1959. 2 figs., 15 refs.

The authors, working at the California Institute of Technology, Pasadena, have shown that the acquisition of skin-reactive properties (that is, the ability to increase local permeability of guinea-pig skin on injection) by soluble antigen-antibody complexes is accompanied by changes in optical rotation. Using complexes with different proportions of antibody and antigen they found that skin reactivity increased in parallel with an increase in laevo-rotation. Complexes in which two molecules of antigen were combined with one of antibody were not skin-reactive, and their formation was not accompanied by changes in optical activity. Complexes in which the ratio of antigen to antibody was 3:2 or less were reactive. Because of this the authors suggest that when two or more antibody molecules are combined with the same antigen molecule, as they would be in the latter type of complex, they produce a mutual distortion which is responsible for the toxicity of the complex and for its change in optical activity. *M. C. Berenbaum*

808. Studies on the Development of Complement Fixing Antibodies in Measles Patients. Observations during a Measles Epidemic in Greenland

V. BECH. *Journal of Immunology* [J. Immunol.] 83, 267-275, Sept., 1959. 6 figs., 17 refs.

The occurrence of a measles epidemic in 1955 in a community in Greenland that had not been exposed to the disease before enabled the development of complement-fixing antibodies to be studied in a comparatively large number of cases, 212 sera from 71 patients being examined at the State Serum Institute, Copenhagen. The blood samples were collected at various times from 4 days before the onset of the rash to 60 days afterwards. Measles virus grown in Rhesus kidney tissue culture was used as the antigen.

Sera collected before the appearance of the rash did not contain measurable antibodies. The titres rose sharply after the development of the exanthem, reaching 1:8 to 1:512 by the 2nd day. Maximum titres (1:64 to 1:1,024) were reached 5 days after the onset of the rash, were maintained at this level for about a further 7 weeks, and then slowly declined. Six immune contacts of patients were also examined. Sera obtained on the

day of appearance of the patients' exanthemata had titres of 1:8 to 1:64, and in no case was there any rise in titre 10 to 16 days later. The possibility is pointed out, however, that the antibody titre in persons immune to measles may rise very rapidly after exposure to the virus and may have reached a steady level by the time the rash appears in non-immune patients exposed at the same time.

[It is not often that the opportunity arises, as it has done here, to study the natural history of a common human infectious disease on a large scale in circumstances relatively uncomplicated by pre-existing immunity.] *M. C. Berenbaum*

809. A Microflocculation Test for Poliomyelitis with Observations on the Flocculating Antibody Response in Human Poliomyelitis

N. J. SCHMIDT and E. H. LENNETTE. *American Journal of Hygiene* [Amer. J. Hyg.] 70, 51-65, July, 1959. 18 refs.

Direct flocculation between immune sera and antigens of poliomyelitis virus has recently been used in the serological diagnosis of poliomyelitis. In this paper from the California State Department of Public Health, Berkeley, a study is reported of the value of a modification of the microfloculation test of Smith *et al.* (*Lancet*, 1956, 2, 163; *Abstr. Wld Med.*, 1956, 20, 426) in the diagnosis of poliomyelitis in human beings. The present authors found that it was possible to concentrate the infected tissue-culture fluids from which the antigens were prepared by a procedure called "pervaporation". After dialysis of the supernatant fluid against distilled water the dialysis bags were exposed to the draught of a fan until the volume of liquid was reduced to one-fiftieth of the original volume. This concentrate was then dialysed against physiological saline for 18 to 25 hours at 4° C. Serological tests were carried out with standardized antigens prepared in this way by a microtechnique in which one volume (0.02 ml.) of antigen was added to a unit volume of serum dilution in the cups of a glass plate. This was incubated at 37° C. in a humidified box for 18 hours and the contents of the cups observed under the low power of the microscope for the presence of floccules. With this test fourfold or greater rises in antibody titre were detected in 27 out of 53 cases of poliomyelitis, whereas similar rises were detected by the complement-fixation test in 36 of the 53 cases. A combination of both tests showed serological evidence of infection in 44 cases, whereas when a neutralization test was combined with the complement-fixation test the number of cases showing evidence of infection was 40. The authors state that the microfloculation test appears to be comparable with the complement-fixation test as regards type-specificity and has the advantage that antibodies are detected earlier in the course of the disease than is the case with the complement-fixation test. However, the microfloculation test is expensive of material and labour, especially in the preparation of suitable antigens. Its chief value at present would appear to be as an adjunct to the complement-fixation and neutralization tests. *J. E. M. Whitehead*

Pharmacology and Therapeutics

810. Sustained Release of Drugs in Certain Drug-Resin Complexes as Judged by Urinary Excretion Rates
D. G. CHAPMAN, K. G. SHENOY, and J. A. CAMPBELL. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 81, 470-477, Sept. 15, 1959. 7 figs., 20 refs.

In an investigation carried out in the Department of National Health and Welfare, Ottawa, the urinary excretion of creatinine, of acetylsalicylic acid, and of amphetamine was used as a measure of the physiological availability of these drugs when given in various forms. The normal excretion of creatinine was determined for a 24-hour period in 10 subjects. When these control figures were subtracted from those obtained after a dose of 1 g. of creatinine in solution or after a dose of creatinine resinate containing the equivalent amount of creatinine it was found that less creatinine was available when it was given in the form of the resinate than when it was given in solution. No evidence was obtained of a sustained effect with the resinate. Excretion of acetylsalicylic acid ingested in the form of a compressed tablet having a disintegration time *in vitro* of one minute was compared with that of the same drug taken in the form of a resin complex. Approximately 100% of the acetylsalicylic acid was available from the resin complex, but there was no evidence of a significant sustained excretion of the drug. The excretion of 10 mg. of amphetamine given in solution was compared with that of equivalent amounts of the drug given in the form of resin complexes of either D-amphetamine sulphate or a mixture of D and DL forms; 91% of the amphetamine was available from both resin complexes. There was no evidence of sustained excretion of the D-amphetamine resinate, but the excretion of amphetamine from the resinate containing the mixture of D and DL amphetamine was sustained to some extent. A test *in vitro* of the two amphetamine resinates did not demonstrate any difference between them in respect of the rates at which they were released from the complex.

P. A. Nasmyth

811. Further Use of Color Coding in Drug Evaluations: Parabromdylamine in Perennial Allergic Rhinitis

I. W. SCHILLER and F. C. LOWELL. *New England Journal of Medicine* [New Engl. J. Med.] 261, 478-482, Sept. 3, 1959. 1 fig., 6 refs.

The authors describe a clinical trial of two antihistamine drugs by a colour-code technique which is considered to give information equal to that obtained by the conventional double-blind method, the colour code being unknown to patients and doctors. The trial was carried out on 38 patients with mild to moderate perennial rhinitis, each of whom was given a bottle containing tablets of a placebo, parabromdylamine, and chlorphenpyridamine, the tablets of each compound being of a different colour. It was made clear that all the tablets were intended for the relief of rhinitis. Each patient

chose one colour of tablet and continued taking this at 4-hourly intervals until the supply was exhausted; if no relief was obtained within 1 to 2 days tablets of another colour were taken, this procedure being continued until all three preparations had been tried. The patient recorded the relief obtained with each preparation and noted any side-effects. A second bottle containing the same three drugs prepared in accordance with a different colour code was then given to each patient, the same routine being followed.

The responses were scored numerically on a clinical basis. In both trials parabromdylamine and chlorphenpyridamine were equally effective, while the placebo was the least effective. Statistical analysis showed a high degree of correlation between the results of the two trials, thus confirming the value of the colour-code technique in comparative clinical trials of different drugs.

T. J. Thomson

812. Gastric Hydrochloric Acid Secretory Response to Orally Administered Betazole Hydrochloride

H. L. SEGAL, C. R. SHEPARDSON, and G. L. PLAIN. *New England Journal of Medicine* [New Engl. J. Med.] 261, 542-544, Sept. 10, 1959. 2 figs., 6 refs.

It has been shown by Kirsner and Ford (*J. Lab. clin. Med.*, 1955, 46, 307; *Abstr. Wld Med.*, 1956, 19, 207) that 3- β -aminoethyl pyrazole (betazole hydrochloride), a substance with a structural resemblance to histamine, is a more powerful but less toxic gastric stimulant than the latter, while more recent experimental work in animals has indicated that it produces strong stimulation of gastric secretion while causing minimal histaminic side-effects.

In the present study, undertaken at the University of Rochester School of Medicine, New York, in a search for a more potent gastric stimulant than caffeine for the detection of achlorhydria by tubeless gastric analysis, 13 healthy subjects were given betazole in doses of 50 mg. subcutaneously and 50 or 100 mg. orally. Samples of gastric juice showed that the stimulation of output of hydrochloric acid by 50 mg. given subcutaneously was slightly less than that produced by 100 mg. by mouth. Flushing was usual with these doses, but the only other side-effect was a mild headache experienced by 2 of the 13 subjects.

D. A. K. Black

813. Detection of Achlorhydria by Tubeless Gastric Analysis with Betazole Hydrochloride as the Gastric Stimulant

H. L. SEGAL, J. C. RUMBOLD, B. L. FRIEDMAN, and M. M. FINIGAN. *New England Journal of Medicine* [New Engl. J. Med.] 261, 544-546, Sept. 10, 1959. 2 figs., 6 refs.

Using the technique of tubeless gastric analysis with an azure-A resin, the effect of betazole hydrochloride as a gastric stimulant [see Abstract 812] was observed

at the Municipal Hospital, Rochester, New York, in 215 subjects who were apparently achlorhydric when caffeine was used as the stimulant. Of these patients 51% gave evidence of hydrochloric acid secretion after the betazole stimulus. It is concluded that betazole in an oral dose of 50 mg. is a more potent gastric stimulant than 500 mg. of caffeine sodium benzoate. Side-effects consisted in mild headache, which occurred in 3%, and "a slight flush" in 13% of the patients.

D. A. K. Black

814. A New Preparation—the Dry Extract of a Species of *Leontice*—for the Treatment of Gastric Disorders with Hypoacidity. (О терапевтической эффективности нового препарата сухого экстракта отавника при заболеваниях желудка с пониженной кислотностью)

T. S. MNACAKANOV and R. S. MAMIKONJAN. *Терпевтичский Архив* [Ter. Arh.] 31, 64–67, Aug., 1959. 1 ref.

The water-soluble dry extract of a species of *Leontice*, when taken in doses of 0.5 g. 10 to 20 minutes before meals, morning and evening, was found to increase gastric acidity in patients suffering from gastric hypoacidity. The course of treatment lasted on average for 10 to 15 days.

The improvement produced by the drug was both subjective and objective and was usually already noticeable 2 to 5 days after the start of treatment. It was maintained for 6 to 18 months, provided the patient was careful with his diet. In cases of relapse of the hypoacidity the treatment may be repeated. A. Orley

[According to additional information received from one of the authors the plant mentioned is *Leontice smirnovi* of the Family *Berberidaceae*, and is to be found only in Soviet Georgia in the Caucasus.—EDITOR.]

815. Effect of Digoxin on the Circulation in Normal Man

A. SELZER, H. N. HULTGREN, C. L. EBNOTHER, H. W. BRADLEY, and A. O. STONE. *British Heart Journal* [Brit. Heart J.] 21, 335–342, July [received Sept.], 1959. 1 fig., 18 refs.

A study of the effect of digoxin on cardiac rate and output, central venous pressure, and arterial pressure in 12 normal subjects is reported in this paper from the Veterans Administration Hospital and Stanford University School of Medicine, San Francisco. Central venous pressure and cardiac output were assessed by cardiac catheterization and the Fick principle, and arterial pressure recorded from the brachial artery. Digoxin was injected directly into the right atrium through the catheter in a dose of 1.25 to 2 mg. over 5 minutes. All determinations were made simultaneously twice before and twice after the administration of the digoxin. Additional observations relevant to the present study were made in a number of other patients to assess the consistency of blood samples taken from the right atrium (in view of the possible effect of streamlining) and also the effect of recumbency on the central venous pressure.

No significant change in mean cardiac output, heart rate, right atrial pressure, or arterial pressure resulted from the administration of digoxin. In the first ancillary study a high degree of reproducibility was found in right atrial samples, and the second study showed a tendency for the right atrial pressure to fall with recumbency.

A review is given of previous work on the haemodynamic effects of digoxin on the normal circulation, in which it has been stated that digoxin lowers the cardiac output and central venous pressure. But the authors point out that these studies were based on slow digitalization over a period of days, when other factors could influence cardiac output, and also employed older and less sensitive techniques of measurement. They conclude therefore from their study that digoxin has no significant haemodynamic effects on the normal circulation.

Gerald Sandler

816. A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs. I. Properties

T. RODMAN, C. S. RYAN, and B. H. PASTOR. *American Journal of Medicine* [Amer. J. Med.] 27, 411–414, Sept., 1959. 3 figs., 6 refs.

A comparative study of the action of the four anticoagulant drugs dicoumarol, prothromadin (warfarin), phenindione, and diphenadione is described from the Veterans Administration Hospital, Philadelphia. The trials were carried out on 80 relatively healthy subjects with no therapeutic indications for anticoagulant therapy who were divided into various different groups.

When large single doses of the four drugs were administered the onset of prothrombin depression appeared after 8 to 16 hours in all cases, maximum depression being reached at 32 hours with phenindione and at 40 hours with the other drugs. The degree of depression was fairly constant with each drug, but the duration of depression varied widely from subject to subject. A comparison between the effects of a large initial dose of dicoumarol and a more gradual induction regimen showed that a large initial dose of 600 mg. on the first day followed by 150 mg. on the second day was more rapidly effective than gradual induction and no excessive prothrombin depression occurred. Optimum induction regimens of the four drugs were then compared in 12 subjects each, a large initial dose varying with the initial prothrombin activity being followed by a maintenance dose. There was no marked difference in effectiveness between the four drugs.

David Phear

817. A Comparative Study of Four Prothrombinopenic Anticoagulant Drugs. II. Clinical Study

T. RODMAN, C. S. RYAN, B. H. PASTOR, and W. J. HOLLENDONNER. *American Journal of Medicine* [Amer. J. Med.] 27, 415–423, Sept., 1959. 1 fig., 10 refs.

A clinical investigation of the 4 anticoagulant drugs previously studied [see Abstract 816] was carried out on 287 patients, the majority (171) of whom were suffering from myocardial infarction. The average period of treatment was 25 days per patient. A single daily dose was given, which was adjusted so as to maintain prothrombin activity at between 10 and 30% of

normal. It was also decided to give a larger initial dose than is customary in order to obtain rapid achievement of therapeutic levels. In only 5 out of 84 patients treated with large induction doses did the prothrombin activity fall below 10% at 64 hours, and in all 5 the level returned spontaneously to within the therapeutic range by 88 hours. For initial induction phenindione had the quickest effect, producing an adequate reduction of prothrombin activity at 40 hours in 100% of patients receiving it compared with 71% of those given dicoumarol and 84% of those given diphenadione. Dicoumarol and diphenadione produced more stable levels of prothrombin activity than did prothromadin and phenindione.

Major haemorrhage occurred in 6 patients (2%) and minor haemorrhage in 17 (6%). Of these 23 episodes of bleeding, 19 occurred while prothrombin activity was within the therapeutic range and 4 while it was below 10%. In 2 patients with severe chronic congestive failure massive gastro-intestinal haemorrhage contributed to death. It is concluded that all four drugs are satisfactory prothrombinopenic agents. However, the prothrombin activity was more easily maintained within the therapeutic range with dicoumarol and diphenadione than with the other two anticoagulants.

David Phear

818. Acute Pancreatitis in Patients Receiving Chlorothiazide

D. H. JOHNSTON and A. L. CORNISH. *Journal of the American Medical Association [J. Amer. med. Ass.]* 170, 2054-2056, Aug. 22, 1959. 5 refs.

Over a recent 12-month period the authors, at the Lexington Clinic, Kentucky, have seen 4 patients (3 female and 1 male, aged 52 to 84 years) suffering from acute pancreatitis, all of whom had been receiving chlorothiazide for several months. The diagnosis of acute pancreatitis was established in all the cases on clinical and biochemical grounds and was confirmed pathologically in the one fatal case. The dosages of chlorothiazide administered to the patients before the onset of pancreatitis were, respectively, 1 g. daily for 3 months, 0.5 g. daily for 4 months, 0.5 g. daily for 3 months, and 1 g. once or twice a week for 15 months. There was no evidence of gall-bladder disease or of alcoholism in any of the patients.

The authors consider that the development of acute pancreatitis in these patients may have been more than a coincidence, and hope that by reporting these cases they may draw the attention of others to the possible development of pancreatitis in patients who receive chlorothiazide.

Bernard Isaacs

819. Hydroflumethiazide—a New Oral Diuretic

C. J. EDMONDS and G. M. WILSON. *Lancet [Lancet]* 2, 303-308, Sept. 12, 1959. 6 figs., 13 refs.

The effects of two new oral diuretic preparations, hydroflumethiazide and hydrochlorothiazide, were compared with that of chlorothiazide—to which they are chemically related—in 2 healthy subjects, 28 patients with heart failure, one patient with nephrosis, and one with cirrhosis. Hydroflumethiazide was found to be at least ten times as active, weight for weight, as chlorothiazide,

and a smaller amount was therefore required for treatment. The standard dosage of hydroflumethiazide in the present series was 50 mg. 3 times a day initially, with 50 mg. daily for maintenance. Hydrochlorothiazide was as effective as hydroflumethiazide.

Hydroflumethiazide increased sodium excretion for 10 hours, whereas even with large doses of chlorothiazide sodium diuresis ceased after 6 hours. Potassium excretion was increased by both drugs, but more intensely by chlorothiazide. Hypokalaemia occurred in some patients given hydroflumethiazide, but was easily corrected by administration of potassium chloride in a dosage of 1 g. 3 times daily. No other significant side-effects were observed. In some cases of heart failure there was no response to either chlorothiazide or hydroflumethiazide, but a good diuresis was obtained with mercurial diuretics. The authors consider that hydroflumethiazide in small doses, with its negligible carbonic anhydrase inhibiting action, is probably preferable to chlorothiazide in cases of cirrhosis of the liver where carbonic anhydrase inhibition may contribute to coma.

David Phear

820. The Diuretic Activity of Hydroflumethiazide

A. C. KENNEDY, W. C. WATSON, and C. CUNNINGHAM. *Lancet [Lancet]* 2, 309-311, Sept. 12, 1959. 1 fig., 8 refs.

The diuretic effect of a dose of 200 mg. of hydroflumethiazide was studied on 31 occasions at the Royal Infirmary, Glasgow, in 17 patients, 13 of whom had congestive heart failure, one cirrhosis of the liver, one nephrosis, one oedema of unknown aetiology, and one had no oedema. The drug was given by mouth. Detailed biochemical and volumetric studies were carried out in 14 cases, in one of which two doses had been given, while in the 3 remaining cases only the urine volume was measured.

A single dose of 200 mg. of hydroflumethiazide by mouth was found to be as effective as 2 g. of chlorothiazide by mouth or 2 ml. of mersalyl by intramuscular injection. There was a marked increase in the volume of urine which was associated with increased excretion of sodium chloride and, to a lesser extent, of potassium. Usually the diuresis was over within 12 hours, but in several patients, including one with hepatic cirrhosis, it continued into the following day. No toxic effects were observed.

David Phear

821. Hydroflumethiazide—a New Oral Diuretic

C. R. BLAGG. *Lancet [Lancet]* 2, 311-313, Sept. 12, 1959. 4 figs., 10 refs.

The author reports from the University of Leeds a comparative study of the diuretic action of hydroflumethiazide and chlorothiazide in 3 healthy subjects and 13 patients with oedema. It was found that in healthy subjects 150 to 200 mg. of hydroflumethiazide caused a marked diuresis, with considerable increases in sodium and chloride excretion and a variable but marked increase in potassium excretion. The pattern of excretion after administration of chlorothiazide was similar, and comparison of the drugs indicated that the effect of 100 to 150 mg. of hydroflumethiazide was equivalent to that of 0.5 g. of chlorothiazide. With either drug diuresis began

within 2 hours and had not always fully subsided after 12 hours. There were two peaks in diuresis, one after 4 hours and the other after 8 to 9 hours, the first peak being associated with a rise in urinary pH and probably being due to an initial carbonic anhydrase inhibitory effect.

In 12 patients with congestive heart failure and in one with nephrosis a satisfactory diuresis occurred after administration of hydroflumethiazide. Epigastric pain occurred in 2 patients, suggesting that the drug should be given after meals. There was a marked fall in the serum potassium level in 2 patients, and digitalis intoxication developed in one patient with heart failure. In 2 patients with malignant hypertension who were receiving ganglion-blocking agents the hypotensive effect of hydroflumethiazide was comparable to that obtained with an equivalent dose of chlorothiazide. The former drug had no effect on the blood pressure of normotensive subjects.

David Phear

822. Human Pharmacology of Thiazide Derivatives. [Review Article]

J. H. MOYER. *Journal of the American Medical Association* [J. Amer. med. Ass.] 170, 2048-2054, Aug. 22, 1959. 9 figs., 7 refs.

823. A Comparison of Hypnotic and Residual Psychological Effects of Single Doses of Chlorpromazine and Secobarbital in Man

C. KORNETSKY, T. S. VATES, and E. K. KESSLER. *Journal of Pharmacology and Experimental Therapeutics* [J. Pharmacol. exp. Ther.] 127, 51-54, Sept., 1959. 3 figs., 8 refs.

The subjects taking part in this series of experiments reported from the National Institute of Mental Health, Bethesda, Maryland, were 18 healthy young volunteers and the drugs used were chlorpromazine and secobarbital (quinalbarbitone); these were given first in doses of 100 mg. and then of 200 mg. at 7 p.m., alternating with a lactose placebo in conformity with a latin-square design, in the form of identical tablets to groups of 6 subjects on 3 consecutive nights in each of 2 consecutive weeks. For the 12 hours following each dose a record of the subject's sleep was made by a nurse every half-hour. Next morning, that is, between 14 and 15 hours after medication, all the patients were subjected to three brief performance tests, namely, the digit-symbol substitution test, the symbol copying test, and the tapping speed test.

The results indicated that both doses of chlorpromazine and the higher dose of quinalbarbitone produced a significant increase in mean sleeping time: after the placebo this was 6.93 hours, after 100 mg. of quinalbarbitone 7.44 hours, after 200 mg. of quinalbarbitone 8.14 hours, and after 100 and 200 mg. of chlorpromazine the times were 8.72 and 8.97 hours respectively. In the performance tests the scores after 200 mg. of chlorpromazine and 200 mg. of quinalbarbitone were significantly lower than those after the placebo in all three tests, while 100 mg. of chlorpromazine produced a significantly lower score than the placebo in the tapping

speed and symbol copying tests; however, 100 mg. of quinalbarbitone had no significant effect on any of the test results. The residual effect seen with the higher doses supports the notion of a "hangover" effect after chlorpromazine and barbiturate administration.

I. M. Rollo

824. Some Observations on a Sedative and a Tranquillizing Agent

C. H. SCHEIFLEY. *Proceedings of the Staff Meetings of the Mayo Clinic* [Proc. Mayo Clin.] 34, 408-419, Aug. 19, 1959. 10 refs.

Since 1955 "plexonal", a combination of three barbiturates, scopolamine, and dihydroergotamine in minimum doses, has been given as a sedative to a total of 700 patients suffering from various cardiac disorders, with satisfactory results. More recently 72 patients have been given either plexonal or meprobamate, both drugs in tablet form being available to each patient. Of the 72 patients, 53 preferred plexonal, 8 preferred meprobamate, and 11 considered that the two drugs were equally effective. Side-effects of meprobamate included lassitude and nervousness in 5 patients and nausea in 2; there were no similar side-effects of plexonal, but one patient complained of headache. There were allergic reactions to plexonal in 2 cases and to meprobamate in 2, the reactions to the latter being the more severe.

V. J. Woolley

825. Studies in Postural Hypotension following Ganglion Blocking Drugs

T. V. O'DONNELL. *Clinical Science* [Clin. Sci.] 18, 237-249, May [received Sept.], 1959. 5 figs., 21 refs.

In a study of the mode of development of postural hypotension after the use of ganglion-blocking drugs carried out at the University of Otago, New Zealand, hexamethonium bromide in a dose of either 10 or 20 mg. was administered intravenously to 14 hypertensive patients and 9 normotensive subjects, the tilting table being used to induce varying degrees of postural hypotension. Recordings were made of the arterial blood pressure, plasma volume, cardiac output, and lower leg volume before and during tilting. The methods employed are fully described.

The degree of postural hypotension was shown to depend on the dose of hexamethonium and the duration and angle of head-up tilting. After administration of hexamethonium blood pooled in the legs and such pooling was exaggerated on tilting the subject. Tilting caused a fall in cardiac output, which was usually greater after hexamethonium, although the reduction in output could not be directly correlated with the magnitude of the fall in blood pressure produced. Spontaneous postural hypotension often occurred when the blood volume was reduced by venesection or by sodium restriction. In these conditions the tendency to postural hypotension was considerably enhanced when the nervous pathways of the homeostatic reflexes were blocked by hexamethonium. On the other hand an increase in blood volume produced by an infusion of dextran solution diminished the ability of hexamethonium to cause postural hypotension.

W. C. Bowman

Infectious Diseases

826. Studies of Variations of Glutamic-oxalacetic Transaminase in Serum in Infectious Hepatitis

A. J. SCHNEIDER and J. W. MOSLEY. *Pediatrics* [Pediatrics] 24, 367-377, Sept., 1959. 3 figs., 9 refs.

In this paper from the U.S. Department of Health, Atlanta, Georgia, a comparative study is reported of the variations in the serum glutamic-oxalacetic transaminase (S.G.O.T.) activity in individuals from 66 families suffering from infective hepatitis, in contacts, and in controls. Some of the controls and the contacts received immune globulin for prophylaxis. From the 66 families a total of 249 individuals were available for study, including 145 under the age of 20 years and 104 over that age. The over-all incidence of abnormality of S.G.O.T. activity was 15.2% in the children and 3.8% in the adults. In jaundiced patients with infective hepatitis S.G.O.T. activity was abnormally high, this high level persisting in many patients for more than 1 to 2 months after the onset of the disease. S.G.O.T. activity was also high in a significant percentage of symptom-free contacts; in one epidemic of infective hepatitis this rise was prevented by administration of immune globulin. There was no correlation between the duration and magnitude of the abnormality of S.G.O.T. activity and the clinical severity of the disease. The authors consider that a rise in S.G.O.T. activity in the contacts of patients with infective hepatitis in the absence of any other condition known to cause such a rise is evidence of a subclinical infection with the virus.

Winston Turner

827. Staphylococcal Pneumonia in Influenza in Relation to Antecedent Staphylococcal Skin Infection

W. R. O. GOSLINGS, J. MULDER, N. MASUREL, and J. DJAJADININGRAT. *Lancet* [Lancet] 2, 428-430, Sept. 26, 1959. 9 refs.

At the University Hospital, Leiden, a study was made of staphylococci from 40 cases of influenza with secondary staphylococcal pneumonia. All but one of the strains were isolated from sputum or necropsy material in cases in which the diagnosis of Asian influenza had been established by virological methods.

It was found that in 57 patients or close contacts an active staphylococcal skin lesion was present until shortly before the development of the staphylococcal pneumonia. In 25 of these cases the strain from the skin lesion was identical with the strain cultured from the sputum or necropsy material, and in 3 in which the skin lesion had healed at the time of investigation a staphylococcus isolated from a nasal swab was identical with the respiratory strain. In 3 instances different strains were isolated. In the remaining 26 cases it was impossible to isolate and identify the causative strain, usually because adequate information was not readily available, but it was assumed that in this group the proportion of those in which the skin or nasal and the respiratory strains

were identical was similar to that in the 31 cases fully investigated. Only about one-third of the persons with skin lesions were patients with pneumonia, the majority being members of patients' families. In 2 cases infection was transmitted to a nurse. Overt lesions were by far the most common.

Strains isolated from patients who had been in hospital for a few days differed in sensitivity and phage type from strains obtained on admission or at necropsy performed within 24 hours of admission. Cultures taken after the first day, especially from necropsy material, not only showed an increased resistance to penicillin and streptomycin, but also contained many more strains resistant to other antibiotics. The most important change in phage type found was a considerable increase in Group-III strains after the first day in hospital.

R. G. Meyer

828. Benign Streptococcal Sore Throat

W. BRUMFITT, F. O'GRADY, and J. D. H. SLATER. *Lancet* [Lancet] 2, 419-423, Sept. 26, 1959. 38 refs.

The carrier rate of throat organisms among army recruits was determined by swabbing their throats within one hour of arrival at their depot and again after living in the depot for 3 to 4 weeks. The carrier rate was also determined at other depots among soldiers sleeping in the same barrack-rooms as men with known streptococcal sore throat. In addition a study was made of patients admitted to the Cambridge Military Hospital, Aldershot, with acute sore throat, but without clinical evidence of more generalized disease, such as glandular fever, of which the sore throat might have been a feature. There did not appear to be an epidemic of acute sore throat during the time the patients were admitted. Of the 242 patients, 135 were treated with aspirin gargles alone and the remaining 107 were treated with penicillin. Re-examination of each patient was carried out 4 to 5 weeks after the onset of the sore throat, with particular reference to symptoms suggestive of rheumatic fever or acute nephritis.

Lancefield Group-A streptococci were isolated from 5 to 11% of 637 recruits (in monthly batches), this figure increasing to 6.5 to 20.5% after 3 to 4 weeks of communal life without cases of sore throat occurring. In contrast the organisms were isolated from 68% of 56 barrack-room contacts and from 57 to 88% of patients admitted to hospital with sore throat. Among these patients streptococcal and non-streptococcal cases were indistinguishable clinically. A significant rise in antistreptolysin-O titre was observed in only 16% of cases from which Group-A streptococci had been isolated. Adenovirus was isolated from 5 of 42 patients. No first attacks of rheumatic fever were observed, though there was one recurrence, and one patient developed acute nephritis.

As the isolation of haemolytic streptococci from patients with acute sore throat does not necessarily

indicate that these organisms are the primary cause of the illness, and as most of the patients in the present series appear to have had a benign streptococcal sore throat in which the streptococci played an opportunist role, it is recommended that penicillin therapy should be used only for patients who have had rheumatic fever previously and in epidemics, in which there may be organisms of enhanced virulence. The dose of penicillin, if given, should be adequate and administered for approximately 7 to 10 days.

R. G. Meyer

829. Treatment of Severe Tetanus

J. R. LAWRENCE and M. J. W. SANDO. *British Medical Journal* [Brit. med. J.] 2, 113-118, Aug. 1, 1959. 2 figs., bibliography.

The chief aim in the treatment of tetanus is to support the patient through the acute attack by controlling muscular spasm and rigidity and preventing respiratory infection. Over a 5-month period 14 cases of tetanus were admitted to the Royal Adelaide Hospital, Australia, 9 being severe, and in this paper the management of these 9 cases is described. Each patient was admitted to a sound-proof room and given 300,000 units of antitetanus serum, "half intravenously". The spasms were controlled by administration of D-tubocurarine and by artificial respiration with a Beaver respirator adjusted to provide positive and negative pressure through a tracheotomy tube. The sedatives found to be most useful were promethazine, pethidine, chlorpromazine, paraldehyde, and chloral. In order to correct dehydration, to nourish the patient, and to administer drugs an intravenous drip was set up. Respiratory infection was controlled by aspiration of secretions, "alevaire" being used if the secretion was very tenacious, by administration of antibiotics, and by prevention of inhalation of pharyngeal contents by means of a cuffed pharyngeal tube. An intragastric polythene tube was used for feeding or for gastric aspiration as necessary. Of the 9 patients, 4 died, including 2 from massive pulmonary embolism and one in acute renal failure. Other complications were bone-marrow depression from prolonged nitrous-oxide anaesthesia, and hyperglycaemia, which was severe enough to necessitate administration of insulin in 3 cases.

Winston Turner

830. Toxoplasmic Encephalopathy—a Form of Meningo-encephalomyelitis in Adult Toxoplasmosis. [In English]

T. HAFSTRÖM. *Acta psychiatrica et neurologica Scandinavica* [Acta psychiat. scand.] 34, 311-321, 1959. 25 refs.

After a review of the relevant literature the author outlines the clinical picture of acute toxoplasmosis, the main features in the adult being high fever, pains in the back, vomiting, and a pale red eruption, followed by enlargement of the regional lymph nodes and spleen. There may also be pneumonia with patchy radiographic opacities and neurological signs and symptoms suggestive of meningo-encephalomyelitis or "toxoplasmic encephalopathy". Among a total of 15 cases of toxoplasmosis seen by the author at Södersjukhuset, Stock-

holm, 6 were considered to be examples of toxoplasmic encephalopathy, and these cases are described in detail. The neurological features, which developed 2 to 9 months after the onset of the disease in most cases, included depression, anxiety, vertigo, headache, and paraesthesiae of the arms and legs. The cerebrospinal fluid was often normal, but there was usually enlargement of the cervical lymph nodes. No treatment is mentioned, the symptoms generally improving over a period of months or years.

G. S. Crockett

831. The Spread of *Candida* in Infants and Children

S. VINCE. *Medical Journal of Australia* [Med. J. Aust.] 2, 143-145, Aug. 1, 1959. 34 refs.

The percentages of healthy infants and children and of children in hospital who harbour *Candida* were studied in 500 children in Budapest, Hungary, and 436 in Sydney, Australia. Direct smear examination of oral swabs showed that 17% of healthy newborn infants in Sydney and 19% of similar infants in Budapest harbour *Candida*. In all healthy and normal children the proportions were 17% and 16% respectively. Among children in hospital the percentages were much higher; culture of oral swabs was positive in 49% of these children in Budapest and 25% of those in Sydney, the difference being attributed to overcrowding of hospitals, lack of staff, and generally poor hygienic and nursing conditions in Budapest.

Specimens of blood and urine from 60 infants in Budapest who had received broad-spectrum antibiotics were cultured. In 3 cases cultures positive for *Candida* were obtained from the blood and in 19 from the urine. It is stressed that too much blind reliance should not be placed on these mycological findings because a positive culture, even from the blood, does not necessarily signify an infection requiring treatment.

John Fry

832. Generalized Endogenous Mycosis in Childhood

S. VINCE. *Medical Journal of Australia* [Med. J. Aust.] 2, 145-149, Aug. 1, 1959. 34 refs.

The pathogenesis and diagnosis of generalized endogenous mycosis due to *Candida albicans* are discussed with reference to 8 cases seen in Budapest and one in Sydney. The primary illness in these patients, all of whom were under 2 years of age, was respiratory infection in 6, enteritis in one, ear infection in one, and hydrocephalus in one. The diagnosis of endogenous mycosis is often difficult, since *Candida* can be isolated from as many as 25 to 50% of all children in hospital, and even the presence of the fungus in the blood, urine, or cerebrospinal fluid does not necessarily mean that a generalized infection is present. The patients in the present series were considered to be infected because the fungus was isolated from a number of different sites.

The generalized spread of *Candida* in these cases was considered to be due to a lowering of general resistance and the use of antibiotics (all the patients had had at least one antibiotic). There were 2 deaths in the series, the remaining patients improving with administration of nystatin, para-aminobenzoic acid ester, and gamma globulin, alone or in various combinations.

John Fry

Tuberculosis

833. Isoniazid and para-Aminosalicylic Acid Toxicity in 513 Cases: a Study Including High Doses of INH and Gastrointestinal Intolerance to PAS

S. J. BERTÉ and H. J. DEWLETT. *Diseases of the Chest* [Dis. Chest] 36, 146-151, Aug., 1959. 11 refs.

The incidence of toxic reactions to high doses of isoniazid and to PAS was studied in 513 patients treated at Valley Forge Army Hospital, Phoenixville, Pennsylvania, between November 1, 1956, and August 1, 1957. All the patients received isoniazid, 184 being given 300 mg. daily and the remainder 10 or 16 mg. per kg. body weight daily together with 100 mg. of pyridoxine daily. PAS in a dosage of 12 g. daily was given to 303 of the 513 patients. Since it is held that many of the gastro-intestinal symptoms usually caused by PAS are due to impurities in the drug, which deteriorates with storage, the authors used sodium PAS not more than 2 months old. This was dispensed in a sealed polyethylene pack, containing the equivalent of 4 g. of PAS, which was opened at the bedside and the contents mixed with water and taken at once.

Toxic reactions to isoniazid occurred in 5 patients receiving the high dosage of the drug, usually during the first month of treatment. These were considered to be allergic reactions, except possibly in 2 cases in which dizziness might have been of neurological origin. Reactions to PAS were noted in 27 cases, again mostly during the first month of treatment, these reactions being due to gastro-intestinal intolerance in 16 and to allergy in the remainder.

The ages of the patients ranged from 20 to 40 years, and the incidence of malnutrition or intercurrent disease was very low. By the end of the period of observation 111 patients had been treated for 1 to 2 months, 133 for 3 to 6 months, and 209 for more than 6 months.

It is concluded that in the treatment of tuberculosis high doses of isoniazid together with PAS can safely be given for prolonged periods provided the patient's nutritional condition is good and there is no disease of the central nervous system or of the liver.

Janet Q. Ballantine

834. B.C.G. and Vole Bacillus Vaccines in the Prevention of Tuberculosis in Adolescents

SECOND REPORT TO THE MEDICAL RESEARCH COUNCIL BY THEIR TUBERCULOSIS VACCINES CLINICAL TRIALS COMMITTEE. *British Medical Journal* [Brit. med. J.] 2, 379-396, Sept. 12, 1959. 2 figs., 26 refs.

A clinical trial to define and compare the extent and duration of the protective effects of B.C.G. and vole bacillus vaccines against tuberculosis in adolescents was started in 1950 and is still in progress. The 56,700 participants were all aged 14 to 15½ years on entry and are now between 21 and 23. Those with positive reactions to tuberculin on entry were not vaccinated; those whose

reaction to 100 units of tuberculin was negative were vaccinated with B.C.G. or vole bacillus vaccine or left unvaccinated, according to a method of random allocation. There were thus five groups of participants: (1) Tuberculin-negative and unvaccinated (13,300). (2) Tuberculin-negative and given B.C.G. vaccine (14,100). (3) Tuberculin-negative and given vole bacillus vaccine (6,700). (4) Positive to 3 tuberculin units (T.U.) and unvaccinated. (5) Negative to 3 T.U. but positive to 100 T.U. and unvaccinated. All the participants, including members of Groups 4 and 5, have been followed up intensively. A detailed description of the plan and conduct of the trial was given in the first report (*Brit. med. J.*, 1956, 1, 413; *Abstr. Wld Med.*, 1956, 20, 102).

A total of 349 cases of definite and 23 of possible tuberculosis occurred among the participants within 5 years of entry. The definite cases were distributed as follows.

Group	Number of Cases	Annual Incidence per 1,000 Participants
1	153	2.29
2	27	0.38
3	11	0.33
4	128	1.61
5	30	0.92

The initial radiographs in these cases showed no important differences between the various groups in respect of the presence of cavitation. There was, however, a suggestion that in the vaccinated subjects the lesions when first detected were, on the average, not so extensive as those in the unvaccinated subjects. As regards the maximum radiographic extent of the pulmonary lesions there was again no evidence of important differences in the incidence of cavitation between the groups. It did appear, however, that the disease was generally rather less extensive in the vaccinated than the unvaccinated. "In other words, the degree of protection from vaccination for the extensive lesions was at least as great as, and may have been greater than, that for the less extensive lesions." In 95% of the definite cases of tuberculosis arising after entry and accepted for this report there was agreement on diagnosis between the assessor and the physician in charge. The average duration of observation of the participants so far is 6½ years and it is clear that the protection given by both vaccines has remained at a high level for at least this length of time.

Direct checks made on representative samples show that the unvaccinated and vaccinated groups were closely similar on entry in their distribution by age, sex, and number of brothers and sisters. Furthermore, cooperation of the participants was similar in all groups. It is concluded that as a result of the many cunningly devised

safeguards with which the trial was operated no serious bias entered into the comparison between the groups and that the difference in incidence of tuberculosis may confidently be attributed to the vaccination. The protection afforded by B.C.G. to the tuberculin-negative section of the population is estimated to lie between 71 and 90% and that by vole bacillus vaccine between 73 and 96%. The strength of the early batches of vole bacillus vaccine was below the standard intended. They nevertheless conferred substantial protection against tuberculosis, and lupus vulgaris at the site of vaccination (noted in the first report) did not occur with these batches.

The intention is to continue this trial in its present form into 1960.

[It is not possible to reflect the importance of this report in an abstract. Careful study of the whole is essential.]

Norman F. Smith

RESPIRATORY TUBERCULOSIS

835. Allergic and Toxic Reactions of Prolonged Chemotherapy for Pulmonary Tuberculosis

B. T. FEIN. *Diseases of the Chest* [Dis. Chest] 36, 286-292, Sept., 1959. 16 refs.

The type and time of onset of allergic and toxic reactions to prolonged chemotherapy for pulmonary tuberculosis were studied in patients attending the City of San Antonio Public Health Chest Clinic, Texas. During the years 1954 to 1956 reactions were observed in 100 cases, and were classified as follows: deafness (17), vertigo (12), urticaria (10), angio-oedema (4), anaphylactoid (3), headache (14), gastro-intestinal upset (11), peripheral neuritis (9), nervousness and insomnia (2), eczema (7), pityriasis rosea (1), severe anaemia (3), granulocytopenia (2), rheumatoid arthritis (4), and jaundice (1). The incidence of reactions was highest in the first 6 months of treatment (33 cases); in the second 6 months they occurred in 16 cases, in the third in 19, and in the fourth in 14. After 2 years' treatment reactions were noted in only 18 cases. At the time the reactions developed 83 patients were receiving streptomycin and isoniazid, 14 streptomycin and PAS, and 3 PAS and isoniazid. The reactions were most severe in the first year of treatment.

These findings indicate that reactions are not an important consideration in the prolonged chemotherapy of pulmonary tuberculosis.

B. Golberg

836. The Behaviour of 306 Tuberculous Cavities Treated by Chemotherapy. Factors in Prognosis. (Devenir de 306 cavernes tuberculeuses traitées par la chimiothérapie. Éléments du pronostic)

P. PUECH, J. HARDRE, C. ACKERMANN, and J. L. SIMONIN. *Revue de tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 23, 685-702, July [received Oct.], 1959. 10 refs.

This report is based on a follow-up study of 265 students aged 18 to 30 who were admitted to the students' sanatorium at St. Hilaire-du-Touvet, Isère, between January, 1954, and August, 1957, for the treatment of active pulmonary tuberculosis. Excavated lesions were

present in all cases, the total number of cavities being 306. These patients, who represented 22.5% of all those admitted during the period, were followed up for 2 years from the beginning of antibiotic treatment. During this period progress was assessed on the basis of the clinical, radiological, and bacteriological findings at 9, 12, 18, and 24 months. A surprising finding was the persistence of 35.9% of the cavities after 9 months' treatment.

At the end of the 2 years the final assessment was made only on those cases (78% of the total) treated by purely medical measures; of these cases the radiological picture was considered satisfactory in 98.1%. The authors do not consider that the position or size of the cavities or degree of adjacent infiltration has any great bearing on the results, while age of the lesion or previous treatment is only of relative interest. By far the most important factor in their opinion is the rapid elimination of tubercle bacilli from the sputum, and this is largely dependent on the type of treatment given in the first 2 months. Of these patients, 68% had received all three of the usual anti-tuberculous drugs, streptomycin, isoniazid, and PAS.

Paul B. Woolley

837. Treatment of Pulmonary Tuberculosis with Isoniazid and Pyrazinamide: Experience in 114 Cases

M. J. SMALL. *Diseases of the Chest* [Dis. Chest] 36, 265-279, Sept., 1959. 4 figs., 19 refs.

At the Veterans Administration Hospital, East Orange, New Jersey, 114 patients with pulmonary tuberculosis were given a combination of 300 mg. of isoniazid and 3 g. of pyrazinamide daily for periods of one to 25 months. None of the patients had had pyrazinamide previously and the organisms in those who had received isoniazid were still susceptible to the drug.

Radiological assessment of progress at the fourth month of treatment in 58 cases of moderately or far-advanced disease showed that the condition was worse in only one case. Cavities had reopened in 2 cases by the eighth and thirteenth months of treatment respectively, but sputum culture remained negative in both. Improvement was marked in 22 cases, moderate in 17, and slight in 10, most of those in the last group showing moderate or marked improvement at the eighth and twelfth months. Of the 8 patients in whom there was no change, 3 had very chronic disease and 5 had persistent large cavities in spite of negative bacteriological findings. Cavity closure was achieved in only 4 of 19 cases with cavities measuring 4 cm. or more, but 11 of those with open cavities were culture-negative. The author considers that the latter finding is characteristic of isoniazid-pyrazinamide therapy.

Of the 58 patients, 55 were culture-negative by the fourth month, 44 of them within the first two months; those still culture-positive at the fourth month tended to remain so. The chief drawback to pyrazinamide therapy was hepato-toxicity. Treatment had to be stopped in 17 cases because of an asymptomatic increase in "bromsulphalein" retention or in the serum alkaline-phosphatase level, in 3 cases because of clinical evidence of hepatitis, and in one case on account of anorexia and nausea. One patient became jaundiced and died within

48 hours, death being the result probably of numerous blood transfusions. Hepato-toxicity occurred at any time up to the tenth month.

B. Golberg

838. **Rhythms of Elimination of Tubercle Bacilli in the Sputum, as Shown by Bacillary Counts, and Focal Reactions in the Course of Treatment of Pulmonary Tuberculosis with Streptomycin.** (Rythmes des éliminations bacillaires dans les crachats révélés par la numération des bacilles, et réactions focales au cours du traitement par streptomycine de la tuberculose pulmonaire)

C. MATTEI. *Revue de tuberculose et de pneumologie [Rev. Tuberc. (Paris)]* 23, 501-514, May-June [received Sept.], 1959. 17 figs.

The author describes various patterns of change in the bacterial count of the sputum during the treatment of pulmonary tuberculosis with streptomycin. In some cases there is an immediate fall from several hundreds per field to only a few. Often, however, there is a rise in the count during the first few days of treatment, particularly when cavities are present, from 5 to 10 per field up to 50, 100, or even 500 per field, the numbers gradually decreasing after a few days. In other cases there is a rhythmical rise and fall in the count over several weeks or months, the average count diminishing steadily until negativity is achieved.

In a small proportion of cases a rise in the bacillary count, although it may accompany clinical improvement, is associated with an accentuation and extension of the radiographic opacities and the appearance of new, faint opacities in hitherto unaffected parts of the lung. It is postulated that these represent focal reactions to the toxins released during the massive elimination of tubercle bacilli and caseous material from the lung. The radiographic changes gradually disappear in 3 to 6 weeks.

[How often these various phenomena occur is not stated.]

Arnold Pines

839. **Combined Drug Treatment of Tuberculosis. I. Prevention of Emergence of Mutant Populations of Tubercle Bacilli Resistant to Both Streptomycin and Isoniazid in vitro**

M. L. COHN, G. MIDDLEBROOK, and W. F. RUSSELL JR. *Journal of Clinical Investigation [J. clin. Invest.]* 38, 1349-1355, Aug., 1959. 20 refs.

The authors report from the University of Colorado School of Medicine, Denver, that cultural methods of investigating the frequency of occurrence of mutants resistant to streptomycin and isoniazid among populations of the H37Rv and Pearson-1 strains of tubercle bacilli have shown that approximately 1 in 10^6 may be resistant to streptomycin and 1 in 10^5 resistant to isoniazid. Further experiments indicated that mutants resistant to both drugs simultaneously did not occur in populations of 10^{10} .

Incidental findings were that although high concentrations of isoniazid did not prevent the appearance of resistant strains on media containing concentrations of the drug lower than those known to be effective against streptomycin-sensitive organisms, nevertheless concentrations of isoniazid which were ineffective for the com-

plete inhibition of growth of isoniazid-sensitive organisms were able, in the presence of optimal concentrations of streptomycin, to prevent the growth of isoniazid-resistant organisms. The prevention of emergence of drug-resistant strains is attributed to the cross-sterilizing action of the two drugs on individuals separately resistant to each drug. The clinical implications of these findings are discussed.

J. Robertson Sinton

840. **Combined Drug Treatment of Tuberculosis. II. Studies of Antimicrobially-active Isoniazid and Streptomycin Serum Levels in Adult Tuberculous Patients**

W. MANDEL, A. D. HEATON, G. MIDDLEBROOK, and W. F. RUSSELL JR. *Journal of Clinical Investigation [J. clin. Invest.]* 38, 1356-1365, Aug., 1959. 3 figs., 34 refs.

Investigations carried out at the National Jewish Hospital (University of Colorado School of Medicine), Denver, in patients suffering from pulmonary tuberculosis have revealed that serum concentrations of streptomycin following a single injection of 1 g. of the drug are similar in all patients, and that an effective concentration is still present in the serum after 6 hours. In contrast isoniazid is rapidly inactivated in about 40% of all patients. However, it was shown that its rate of excretion could be delayed by the administration of *p*-aminosalicylic acid or *p*-aminobenzoic acid, although the rate was unaffected by probenecid, phenylbutazone, barbiturates, chlorpromazine, prednisone, sodium salicylate, and pyridoxine.

J. Robertson Sinton

841. **Combined Drug Treatment of Tuberculosis. III. Clinical Application of the Principles of Appropriate and Adequate Chemotherapy to the Treatment of Pulmonary Tuberculosis**

W. F. RUSSELL JR., I. KASS, A. D. HEATON, S. H. DRESSLER, and G. MIDDLEBROOK. *Journal of Clinical Investigation [J. clin. Invest.]* 38, 1366-1375, Aug., 1959. 31 refs.

Experiments described in previous papers [see Abstracts 839 and 840] have suggested that the treatment of pulmonary tuberculosis with a high dosage of streptomycin and isoniazid would give more satisfactory results than the customary routine of giving 1 g. of streptomycin on 3 days a week and 200 mg. of isoniazid daily.

A clinical application of this hypothesis showed that when treated with a dosage of 1 to 2 g. daily of streptomycin (20 mg. per kg. body weight per day) and isoniazid in a dosage of 16 mg. per kg. per day 152 out of 153 tuberculous patients underwent sputum conversion within 6 months, and only one produced streptomycin-resistant organisms. In groups of patients already excreting organisms resistant to both streptomycin and isoniazid or to one of these drugs the results were less satisfactory, and totally resistant organisms appeared in 25% of cases initially sensitive to one or other of the two drugs. The toxic effects of high dosage of isoniazid were sufficiently severe, however, for the authors to suggest that a lower dosage would be preferable.

J. Robertson Sinton

842. Combined Drug Treatment of Tuberculosis. IV. Bacteriologic Studies on the Sputum and Resected Pulmonary Lesions of Tuberculous Patients

A. D. HEATON, W. F. RUSSELL JR., G. MIDDLEBROOK, and J. DENST. *Journal of Clinical Investigation* [J. clin. Invest.] 38, 1376-1383, Aug., 1959. 21 refs.

At the National Jewish Hospital, Denver, Colorado, specimens of resected pulmonary tissue from 220 tuberculous patients were examined for tubercle bacilli by smear and culture. Specimens from patients who had received a high dosage of streptomycin and isoniazid and whose sputum had been negative before operation failed to produce tubercle bacilli on culture, though it was often possible to discover acid-fast bacilli within the specimens, especially those containing blocked cavities. Resistant organisms were detected preoperatively and also in the specimen in all but 2 of 96 cases in which the sputum was positive at the time of operation, and the 2 patients whose specimens did not produce a growth of organisms continued to excrete resistant organisms from their residual disease.

J. Robertson Sinton

843. The Treatment of Pulmonary Tuberculosis with Prednisolone. (Die Behandlung der Lungentuberkulose mit Prednisolon)

U. BALDAMUS and E. G. EWART. *Deutsche medizinische Wochenschrift* [Dtsch. med. Wschr.] 84, 1625-1632, Sept. 4, 1959. 41 refs.

The authors report from the Dr. Heim Sanatorium, Berlin, the results obtained in 85 cases of pulmonary tuberculosis treated concurrently with the usual antituberculous chemotherapeutic drugs and prednisolone. [The paper is essentially a critical discussion of the indications for this combined form of therapy.]

To 14 critically ill patients with widespread haematogenous tuberculosis or persistent haemoptysis prednisolone was administered within a few days of admission and was considered to be life-saving. The authors were particularly impressed by the cessation of haemoptysis and the rapid abatement of pyrexia. Of a further 56 patients whose clinical and radiological condition had deteriorated or remained stationary in spite of intensive chemotherapy for 2 to 4 months the addition of prednisolone resulted in improvement in 39. The need for intensive chemotherapy before contemplating such an additional measure is emphasized. In view of the good results usually obtained with chemotherapy alone the authors are not prepared to commit themselves on the value of prednisolone, administered locally as well as systemically, in 10 cases with exudate, particularly pleural effusion.

The initial daily dose of prednisolone was 20 mg., administered at first intramuscularly to the more desperately ill patients, but given orally as soon as practicable. This dose was reduced gradually after 5 days to a maintenance dose of between 5 and 10 mg., this being maintained for an average period of 3 months. With this regimen no undesirable side-effects were observed. The results are analysed statistically and a number of illustrative cases are reported in some detail.

H. F. Reichenfeld

844. A New Antituberculous Drug: α -Ethylisonicotinic Acid Thioamide or 1314 Th in the Treatment of Pulmonary Tuberculosis. (Un nouveau médicament antituberculeux: le thioamide de l'acide α -éthylisonicotinique ou 1314 Th dans le traitement de la tuberculose pulmonaire)

P. VÉRAN, N. RIST, R. TRICHEREAU, and C. MOIGNETEAU. *Presse médicale* [Presse méd.] 67, 1597-1600, Sept. 19, 1959. 1 fig., 21 refs.

The authors describe their experience with α -ethylisonicotinic acid thioamide (1314 Th; ethioniamide) in the treatment of 55 cases of pulmonary tuberculosis, of which 38 were chronic cases (19 of them of far-advanced disease) and 17 recent infections with cavitation. During the treatment period the former group was observed for 7 to 10 months and the latter for 4 to 6 months. In all cases a second drug was given with 1314 Th to prevent resistance developing, but in no case was isoniazid given; the chronic cases had all become resistant to one or more of the standard drugs. The dose of 1314 Th varied from 0.5 to 1 g. per day depending on body weight, but later in the investigation higher doses of 1.5 g. given as a suppository were tolerated. This drug, first synthesized in 1956, is a gastric irritant, giving rise to a metallic taste in the mouth, nausea, vomiting, and diarrhoea; when given as a suppository, however, there is little digestive upset. Skin reaction usually shows itself as acne.

The authors were impressed with the results: of the 17 recent cases satisfactory results were obtained in 65%, with cure in 5, good or very good results in 6, and a fair result in 3. Of the 19 chronic cases of moderate severity a good or very good result was obtained in 10 (52%), with healing in 2, but of the 19 advanced cases [as would be expected] only 4 (21%) improved to a moderate degree. From their experience the authors recommend that in cases which are still sensitive to isoniazid 1314 Th should be used to reinforce the latter, replacing either streptomycin or PAS; in cases resistant to isoniazid 1314 Th should be substituted for this drug. There is still some difficulty, however, in deciding which drug to use in conjunction with 1314 Th in order to prevent the development of bacillary resistance to it.

Paul B. Woolley

845. 1314 Th in the Surgery of Pulmonary Tuberculosis. (Le 1314 Th dans la chirurgie de la tuberculose pulmonaire)

H. JOLY and J. P. SCHERDING. *Presse médicale* [Presse méd.] 67, 1600-1602, Sept. 19, 1959. 7 refs.

The new drug 1314 Th [see Abstract 844] has been used by the authors at the Station Sanatoriale de Passy in the preparation of tuberculous patients about to undergo surgical treatment. It was always given in conjunction with another chemotherapeutic agent, and of the 53 patients treated all had developed resistance to one or more of the standard drugs. Pulmonary resection was performed in 45 cases and collapse therapy in 8. The dose of 1314 Th was between 0.75 and 1 g. daily, given together with either viomycin or cycloserine, and treatment was maintained when possible for several weeks before operation. In a further group of 18 patients with tuberculous fistulae or other accessible tuberculous lesions

who had become resistant to one of the standard drugs 1314 Th was applied locally in powder form.

In the group subjected to major surgery the outcome was very satisfactory, while in the second group there was rapid healing of the lesions and disappearance of tubercle bacilli. The authors consider that 1314 Th, applied locally, is the most efficacious of the antituberculous drugs.

Paul B. Woolley

846. **Treatment of Cavitory Tuberculosis with 1314 Th (α -Ethylisonicotinic Acid Thioamide).** (Le 1314 Th ou thioamide de l'acide α -éthyl-isonicotinique dans le traitement de la tuberculose cavitaire)

P. VÉRAN, C. MOIGNETEAU, R. TRICHEREAU, and N. RIST. *Revue de tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 23, 533-569, May-June [received Sept.], 1959. 9 figs., 16 refs.

The authors describe their experience in the treatment of pulmonary tuberculosis with 1314 Th (α -ethylisonicotinic acid thioamide). This drug, though an analogue of isoniazid, is not derived from it and appears to have a different antibacterial action so that, with certain exceptions, isoniazid-resistant bacilli are killed by 1314 Th. A series of 55 hospital patients (36 men and 19 women aged 20 to over 50, half of them being chronic alcoholics) have been treated with 1314 Th, 0.5 to 1 g. being given daily by mouth. [This series has been reported briefly elsewhere (see Abstract 844)—EDITOR.]

In 38 patients long-standing lesions were present, with cavities over 5 cm. in diameter in about half. Of these patients, 7 received streptomycin, 1 g. daily or on alternate days, 8 PAS, 15 g. daily, and 11 cycloserine, 0.5 to 1 g. daily, in addition to 1314 Th. To the remainder one or other of these drugs was given at first, but was later withdrawn because of the development of intolerance or resistance. During treatment fever and cough rapidly disappeared and the erythrocyte sedimentation rate became normal in less than 6 months in 81% of cases. However, increase in well-being and gain in weight were not so marked as are seen with isoniazid therapy. The duration of therapy was 6 to 11 months in 26 cases and 3 to 5 months in 12. In nearly half there was at least moderate radiographic improvement, but in one-third there was little or no change. Of 11 patients whose sputum initially contained tubercle bacilli resistant to the second drug used, only in one was the sputum negative at 9 months, the remainder having developed 1314 Th-resistant organisms or died. Of 23 in whom the organisms were initially sensitive to the second drug, the sputum of 11 became persistently negative on culture, in 6 cases for more than 5 months; 8 of the remainder developed 1314 Th resistance, which was attributed to inadequate dosage of PAS or cycloserine due to intolerance or toxicity.

The remaining 17 patients had recent (and usually previously untreated) lesions of moderate or far-advanced extent. [The exact incidence of cavities is not stated.] Of these, 13 were given streptomycin, 1 g. daily for 2 months and every 2 or 3 days afterwards, 3 cycloserine, and one PAS in addition to 1314 Th, the second drug

having to be omitted later in 4 cases. The clinical response was similar to that in the chronic group. In 63% there was moderate or considerable radiological clearing of lesions. In 14 out of 15 cases in which the sputum was initially positive the cultures became persistently negative after 3 to 4 months; in the remaining case primary resistance to PAS, the drug which had been administered with 1314 Th, was found.

Nearly half the patients complained of nausea, often with anorexia, diarrhoea, loss of weight, and a metallic taste in the mouth. These symptoms were usually transient and occurred only during the first month, but in a few cases treatment with 1314 Th had to be abandoned because of their persistence. The side-effects were commonest among alcoholics and patients with very severe tuberculosis. (In a second trial 40 patients, 11 of whom were included in the first trial, were given 1 to 1.5 g. of 1314 Th in the form of rectal suppositories without experiencing any of the above disturbances, while the clinical, radiological, and bacteriological results were equal to those obtained with oral medication.) Assay of the 1314 Th level in the serum gave very variable results in all cases, but the range was much the same after rectal as after oral administration. The authors conclude that 1314 Th is a most promising drug, especially if combined with streptomycin.

Arnold Pines

847. **Macrocydon in the Treatment of Pulmonary Tuberculosis**

D. H. A. BOYD, S. M. STEWART, A. R. SOMNER, J. W. CROFTON, and R. J. W. REES. *Tubercle* [Tubercle (Lond.)] 40, 369-376, Oct., 1959. 19 refs.

The results of a pilot clinical trial of a new anti-tuberculous agent, macrocydon, are given. Previous work had shown that the drug was highly effective in experimental animals. No effect on the patients' clinical condition was observed and the positivity of the sputum was not reduced. A brief discussion of the possible mode of action and toxic effects of the drug is given.—[Authors' summary.]

848. **Results of Treatment of Pneumoconiosis Complicated by Tuberculosis**

J. H. R. RAMSAY and A. PINES. *British Medical Journal* [Brit. med. J.] 2, 345-348, Sept. 5, 1959. 25 refs.

The authors describe experience of the treatment of 25 cases of pneumoconiosis complicated by tuberculosis seen in Bangour Hospital, West Lothian, and the Southfield and City Hospitals, Edinburgh, between 1953 and 1958. Of the 25 patients (aged 44 to 79 years), 17 had anthraco-tuberculosis and 8 had silico-tuberculosis. Tubercle bacilli were present in the sputum in all cases and also in direct smears in many. The radiological appearances in 18 cases were those of breaking-down progressive massive fibrosis.

It was found that with adequate antituberculous therapy all the patients became non-infectious, sputum conversion occurring in 1 to 8 months (average 3.1 months). In more than half the cases there was radiological improvement, but only in one with progressive massive fibrosis was cavity closure obtained. The 13

patients who completed treatment were culture-negative for periods ranging from 1 month to 37 months after cessation of therapy. There were 4 deaths in the series, none due to active tuberculosis. At the time of the report 10 patients were fit for light work.

Treatment, which was given in hospital until sputum cultures were persistently negative, consisted in daily administration of 1 g. of streptomycin, 15 to 20 g. of PAS, and 200 mg. of isoniazid until full drug sensitivity was established, when the dosage of streptomycin was reduced to 1 g. 3 times a week. After discharge from hospital treatment was continued with 10 g. of PAS and 200 mg. of isoniazid daily until drug therapy had been given continuously for at least 2 years.

Janet Q. Ballantine

849. Asian Influenza and Pulmonary Tuberculosis. [In English]

S. LÖFGREN and A. CALLANS. *Acta medica Scandinavica* [*Acta med. scand.*] 164, 523-527, 1959. 21 refs.

Among 204 patients admitted to St. Göran's Hospital, Stockholm, during the 6 months October, 1957, to March, 1958, for progression of pulmonary tuberculosis, there were at least 28 and probably 42 in whom the progression of tuberculosis had directly followed upon an attack of Asian influenza. The findings are in agreement with the observations made during the 1918 epidemic of influenza and show the importance of special care in the follow-up study of cases of tuberculosis after influenza and other intercurrent infections.—[From the authors' summary.]

EXTRA-RESPIRATORY TUBERCULOSIS

850. New Clinical and Radiological Aspects of Intestinal Tuberculosis. (Nouveaux aspects cliniques et radiologiques de la tuberculose intestinale)

C. MARINA-FIOL. *Gastroenterologia* [*Gastroenterologia (Basel)*] 92, 16-29, 1959. 4 figs., 14 refs.

The author has been studying intestinal tuberculosis at the Institute of Clinical and Medical Investigation, Madrid, for the past 17 years. His interest was originally aroused by the large number of patients with pulmonary tuberculosis who also presented gastro-intestinal symptoms, 50 to 90% of those coming to necropsy showing tuberculous lesions in both the lungs and the intestines. Historically, radiology in 1919 succeeded the era of clinical and post-mortem assessment. By 1941 the introduction of the Berg apparatus made it possible to see tuberculous ulceration in the terminal ileum of the living patient.

An extensive review of the literature showed that constipation rather than diarrhoea is the commonest symptom, accompanied by increased anorexia, persistent fever, and pain in the right iliac fossa. These symptoms, however, seldom occur together, but rather in isolation. Furthermore, the advent of chemotherapy has retarded the development of intestinal lesions, greatly changing the classic picture, so that a new problem in diagnosis has been created. The author's purpose is to classify such lesions in the stage of regression or of stability, and

he therefore presents details of 8 illustrative cases. Interpretation of the radiographs is very difficult, since all the lesions are minimal. Apart from the usually accepted "advance guard" appearances (the "alarm nodule"), full value should be given to small retractions of the contours, to the appearance of a double contour, to rigidity of the mucosal folds with granular appearances, and to the disappearance of the folds in a limited zone of the mucosa, all of these being probable signs of intestinal tuberculosis.

Norman F. Smith

851. Treatment of Tuberculous Meningitis

N. L. WRIGHT. *Quarterly Journal of Medicine* [*Quart. J. Med.*] 28, 449-458, July [received Sept.], 1959. 8 refs.

In this paper from the Northern Ireland Fever Hospital, Belfast, a retrospective statistical analysis of 207 cases of tuberculous meningitis treated between 1947 and 1955 is presented, the author's purpose being to examine the problem of the need for intrathecal treatment. The survival rate was higher (83%) among the 54 patients treated in the more recent years with intramuscular streptomycin plus isoniazid or PAS, but without intrathecal treatment, than among the 153 treated earlier with intramuscular and intrathecal streptomycin or dihydrostreptomycin, but without other tuberculostatic drugs (33%). The proportion of early cases was much higher in the group treated more recently. The incidence of residual defects was 70% among survivors treated with streptomycin alone and 40% in those treated with two drugs. [An unstated number of survivors have not been re-examined, though they are included in the figures.] From this evidence the author concludes that "as regards survival from tuberculous meningitis and residual defects following the disease, the intrathecal administration of streptomycin is not essential, and the best treatment consists of intramuscular streptomycin combined with oral isoniazid or PAS, or both".

[The results in the author's series are inferior to those in many others reported in the literature. The paper contains no fresh knowledge, and it glosses over or omits much factual information upon which the statistical analyses are based, so that these cannot be checked. The use of accurate statistical methods on very incomplete basic material is to be deprecated as it may give an air of spurious accuracy to the conclusions arrived at. In fact, the author's conclusions are very questionable. At the most the analysis shows that, working with a much better case material and after a lot of experience had been gained in management, better results were achieved when streptomycin was combined with isoniazid or PAS, even though no intrathecal treatment was used. But it is quite wrong to conclude from this that the latter treatment is "the best", since isoniazid plus streptomycin was not used at all together with intrathecal treatment. Unfortunately, nobody yet knows the "best" treatment for tuberculous meningitis.]

John Lorber

852. Tuberculosis of the Mouth and Throat

R. A. CAWSON. *British Journal of Diseases of the Chest* [*Brit. J. Dis. Chest*] 54, 40-53, Jan., 1960. 2 figs., 43 refs.

Tropical Medicine

853. Acute Anhidrotic Heat Exhaustion

R. BANNISTER. *Lancet* [*Lancet*] 2, 313-316, Sept. 12, 1959. 16 refs.

In a new nomenclature for heat illness proposed by the Medical Research Council three categories are distinguished: heat stroke, heat hyperpyrexia, and anhidrotic heat exhaustion. In this paper from the Royal Army Medical College, London, the author describes an attempt on the basis of this nomenclature to classify all cases of heat illness in the Army in Aden in the two months September and October, 1958, when 70% of all cases occurring during the year were admitted to hospital. A total of 29 cases of heat illness were admitted during the 2 months, including 12 of acute anhidrosis without signs of hyperpyrexia or heat stroke—a type of heat illness which has not previously been recognized.

The 12 patients, who were incompletely acclimatized soldiers without skin disease affecting the sweat glands, experienced sudden diminution or cessation of sweating during or immediately after severe exertion. Sweating was still imperceptible when the patients were admitted to hospital, although the oral temperature (99 to 102° F.; 37.2 to 38.9° C.) was within a range which might be expected to cause maximal sweating and yet was below that necessary to cause cessation of sweating. Some of the patients were confused, and all were drowsy and incapable of further exertion. They were placed in a hospital ward with roof fans and no special measures were taken to cool them. The author considers that recognition of "acute anhidrotic heat exhaustion" is important, since patients in whom it occurs may develop heat stroke if they are exposed to further exertion or greater heat stress.

R. R. Willcox

INFECTIOUS DISEASES

854. The Clinical Course of Dimorphous Macular Leprosy in the Belgian Congo

S. G. BROWNE. *International Journal of Leprosy* [*Int. J. Leprosy*] 27, 103-109, April-June [received Oct.], 1959. 4 figs., 8 refs.

The skin lesions of dimorphous macular leprosy in the rain forest of the Belgian Congo have certain characteristic features; these may be due to the constant high temperatures and high humidity and to the tendency of deeply pigmented skin to over-react to stimuli. The author studied 62 cases of this form of leprosy admitted to Yalisombo Leprosarium, Oriental Province, representing 10% of the total number of cases isolated there. In the domiciliary leprosy service typical dimorphous macular disease accounted for 3.2% of all cases under treatment (5,349), lepromatous leprosy for 20.6%, and tuberculoid disease for 3.5%. In 1957 11.9% of the total population was under treatment for leprosy. In

many of the cases of dimorphous macular leprosy numerous bacilli were found in the macules.

The author states that a diagnosis of dimorphous macular leprosy is suggested by the presence of two or more "incompatibles", especially by the presence of well-defined hypopigmented macules containing numerous bacilli; the edge of the macule is so abrupt that it cannot be termed lepromatous. The first sign is the sudden appearance of a large, well-defined, hypopigmented macule often in the lumbar or scapular region. The border is clear-cut and the lesion is flat. Usually there is no change in size with time, but sometimes the macule spreads to engulf satellite or colonial macules which have developed. The colonial macules are typical of dimorphous leprosy and are usually 1 cm. in diameter. After a variable number of months there is a widespread eruption of secondary lesions of three kinds: (1) lesions similar to the parent macule but smaller; (2) lesions like the colonial macules with vague edges; or (3) minor tuberculoid lesions with slight elevations and slightly raised edges. Further crops of lesions may appear at intervals.

The neurological findings during the stage of the primary macule resemble those in tuberculoid leprosy—namely, loss or reduction of tactile sense, thermal appreciation, sweating, and hair. The secondary macules resemble lepromatous leprosy, with slight loss of tactile sense but not of thermal sense, hairs, or sweating. Trophic effects commonly occur. Bacteriologically, no bacilli are found by the scraped-incision method, but later about 80% of cases become highly positive for *Mycobacterium leprae*, the organism being found in the primary macule and in the nasal mucosa, earlobes, and elsewhere. The satellite macules may be highly positive, and the successive crops of slightly raised macules are usually also highly positive.

[This paper contains further valuable clinical observations which should be studied in the original by those interested. An editorial contributed by H. W. Wade in the same issue of the *International Journal of Leprosy* (p. 157) reviews the subject.] F. Hawking

855. Administration of Pyrimethamine with Folic and Folinic Acids in Human Malaria

M. G. D. HURLEY. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [*Trans. roy. Soc. trop. Med. Hyg.*] 53, 410-411, Sept., 1959. 7 refs.

Various previous studies have suggested that pyrimethamine appears to inhibit the conversion of folic to folinic acid, thus tending to cause macrocytic anaemia when given in prolonged high dosage. As pyrimethamine is now widely used in the treatment of malaria and of toxoplasmic chorio-retinitis it is important to know if the simultaneous administration of folic acid might interfere with its activity. In tests carried out at the M.R.C.

Laboratories, Fajara, Gambia, on native African children heavily infected with malaria due to *Plasmodium falciparum* there was no apparent inhibitory effect on the action of pyrimethamine. It is therefore recommended that it would be wise to combine folic acid with pyrimethamine in the prolonged treatment of toxoplasmosis so as to reduce the risk of causing macrocytic anaemia.

Clement C. Chesterman

856. Potentiation of Pyrimethamine by Sulphadiazine in Human Malaria

M. G. D. HURLEY. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [Trans. roy. Soc. trop. Med. Hyg.] 53, 412-413, Sept., 1959. 6 refs.

Potentiation of the action of pyrimethamine by sulphadiazine was demonstrated by Rollo (*Brit. J. Pharmacol.*, 1955, 10, 208) in the treatment of chicks infected with *Plasmodium gallinaceum* when he showed that $\frac{1}{3}$ of the minimum dose of pyrimethamine plus $\frac{1}{4}$ of that of sulphadiazine produced the same result as a full dose of either drug alone.

The present author has confirmed this finding in *Plasmodium falciparum* infections in native children in Gambia in whom $\frac{1}{10}$ of the "minimum eradicating dose" (M.E.D.) of pyrimethamine plus $\frac{1}{4}$ of the M.E.D. of sulphadiazine were as effective against asexual parasites as the M.E.D. of either drug given separately. The author states that it would be interesting to know whether pyrimethamine-resistant strains of the malaria parasite could be controlled by giving these two drugs together and whether potentiation occurs against sulphonamide-resistant bacteria.

Clement C. Chesterman

857. Studies on Filariasis in Malaya: Treatment of *Wuchereria malayi* Filariasis with Diethylcarbamazine in Single Daily Doses

L. H. TURNER. *Annals of Tropical Medicine and Parasitology* [Ann. trop. Med. Parasit.] 53, 180-188, June [received Sept.], 1959. 2 figs., 9 refs.

In this paper from the Institute for Medical Research, Kuala Lumpur, the author describes the results obtained with diethylcarbamazine in the treatment of filariasis due to infection with the periodic form of *Wuchereria malayi*. A total of 70 subjects from two endemic areas were chosen, the majority of them being microfilaria carriers. The drug was given by mouth once a day in varied dosage, patients with the highest number of microfilariae in the blood receiving the smaller dosages as a precautionary measure against severe side-effects.

With the lower dosages of 0.1, 0.25, or 0.5 mg. per kg. body weight there was considerable individual variation as regards reduction in the microfilaria count, but in general the rate of reduction was slow. Larger doses of 1 and 2 mg. per kg. body reduced the microfilaria count rapidly and the effects were much less variable. When the dosage was high enough to remove microfilariae from the blood of carriers severe febrile reactions occurred, but these were not observed in patients whose blood films were negative for microfilariae. After the febrile reactions had subsided large increases in

the dosage failed to provoke a recurrence of these side-effects. In 15 patients, irrespective of whether microfilariae were present in the blood, minor local reactions such as lymphadenitis or lymphangitis developed even when only small doses were given. The author found that treatment had no appreciable effect on elephantiasis, and although filariasis recurred in several patients, this recurrence may have been due to reinfection.

O. D. Standen

858. Broncho-pulmonary Shunts in *Schistosoma* Cor Pulmonale

H. A. ZAKY, A. R. EL-HENEIDY, I. M. TAWFICK, Y. GEMEL, and A. A. KHADR. *Diseases of the Chest* [Dis. Chest] 36, 164-172, Aug., 1959. 13 figs., 17 refs.

There are two main forms of pulmonary schistosomiasis which often merge into each other, namely, cardiovascular and parenchymatous. The ova, which reach the lesser circulation from the vesical veins, can penetrate the arterioles and cause local necrotizing arteriolar changes leading to obliterative endarteritis in addition to the usual "bilharzial tubercle". The latter is gradually replaced by fibrous tissue. Deposition of eggs is especially prominent in the perihilar areas and in the lower lobes of the lungs. The occluded vessels become canalized by new capillaries which may dilate to form cavernous blood spaces—the so-called "angiomatoids". Obliterative changes also occur in the vasa vasorum of the larger vessels. It is assumed that connexions form through such angiomatous tissue between the pulmonary and bronchial arterial systems.

The fully developed clinical picture of schistosomal cor pulmonale resembles that of interatrial septal defect, there being enlargement of the pulmonary artery and hypertrophy of the right ventricle. Radiologically, there is an increase in the transverse diameter of the heart and a prominent conus arteriosus.

At the Chest Clinic of the University of Alexandria, Egypt, the authors have examined 5 cases of gross cardio-pulmonary schistosomiasis with hepatosplenomegaly and schistosome eggs in the urine or faeces, or both. Cardiac catheterization was performed and oxygen concentrations determined in the pulmonary artery—in the main trunk, in a dilated branch, and in the "prewedged" position of the catheter. Cardiac output was determined by the Fick principle, blood volume by the azovan blue method, and the magnitude of the shunt was estimated by comparison of the oxygen concentrations in blood from the pulmonary artery, from the right ventricle, and from the aorta.

The results are tabulated and detailed descriptions of 3 of the cases are given. All showed a significant rise in the blood oxygen content at different levels towards the periphery along the course of the pulmonary artery, thus suggesting that there must be contact with the bronchial arterial system. The authors conclude that broncho-pulmonary vascular communications probably develop *pari passu* with the formation of the angiomatoid vascular network, but the exact time in the life history of the disease at which such a shunt develops can only be conjectured.

B. G. Maegraith

Allergy

859. Effect of Antigen and Octylamine on Mast Cells and Histamine Content of Sensitized Guinea-pig Tissues

I. MOTA. *Journal of Physiology [J. Physiol. (Lond.)]* 147, 425-436, Oct., 1959. 12 figs., 27 refs.

In the experiments here reported from University College, London, guinea-pigs were first sensitized with egg albumen and 3 weeks later their tissues, chiefly lung and mesentery, were used for mast-cell counts or for measuring either the amount of histamine released or the amount of histamine remaining in the tissue when the antigen-antibody reaction occurred after the addition of the antigen *in vitro*. A series of uniform samples were prepared to test the inhibitory action of various substances on the antigen-antibody reaction and on the release of histamine by the potent histamine liberator octylamine.

Addition of antigen produced alterations in the mast cells in the lung, ileum, uterus, and mesentery and a corresponding release of histamine; granules disappeared from the mast cells, which were also reduced in total number. The changes in the mast cells and the histamine release were both inhibited by incubation of the tissues in the presence of iodoacetate (0.001M) or of phenol (0.005 or 0.01M), by calcium lack induced by means of 0.01% versene, or by previous heating of the tissue to 45° C. or by cooling to 15° C. The addition of octylamine produced alterations in the mast cells which were characterized by an apparent diffusion of the metachromatic material from the granules; the histamine release accompanying the mast-cell changes was not inhibited by the various inhibitors of anaphylaxis mentioned above.

The author suggests that the rapid disappearance of mast-cell granules as a result of the antigen-antibody reaction may be mediated through lysis induced by activation of an enzyme, since as it is inhibited by metabolic inhibitors and is dependent on temperature, whereas the mast-cell changes induced by octylamine may result from direct combination of this base with the metachromatic material in the granules. G. B. West

860. Manganese Abietate in the Treatment of Allergic Diseases and the Modification of the Terrain on Which They Develop. (L'abietate de manganese dans le traitement des affections allergiques et la modification du terrain sur lequel elles se manifestent)

H. BOUR and R. MELHEN. *Presse médicale [Presse méd.]* 67, 1700-1703, Oct. 3, 1959. 21 refs.

The authors have given courses of up to 20 intramuscular injections of a complex of manganese and abietic acid to about a dozen allergic patients suffering from asthma, migraine, or eczema. Abietic acid is obtained from the resin of various species of pine and consists of derivatives of phenanthrene. When combined with manganese the product is said to be non-toxic. It was given by deep injection in an oily solution containing

0.5% of the compound, an ampoule of 2 ml. thus providing about 690 µg. The authors claim that it is possible to change the properties of plasma in these patients so that the proteolysis of the allergic reaction is reduced and liberation of histamine is prevented. Experience of this substance is as yet too recent and too limited to allow of any firm conclusion, but in the few patients so far treated the clinical results appear to be excellent and long-lasting. G. B. West

861. Dexamethasone Therapy in Bronchial Asthma

J. DUVENCI, S. CHODOSH, and M. S. SEGAL. *Annals of Allergy [Ann. Allergy]* 17, 695-700, Sept.-Oct., 1959. 1 fig., 5 refs.

Dexamethasone (16α-methyl-9α-fluoroprednisolone) was used at the Boston City Hospital (Tufts University School of Medicine) in the treatment of 41 patients with bronchial asthma, 25 of whom had previously been treated with triamcinolone and 6 with prednisolone. The therapeutic results and side-effects were about the same as with the other steroids, but the effective dose of dexamethasone was about one-quarter of that of triamcinolone previously used and one-fourteenth of that of prednisolone. The average maintenance dose of dexamethasone was 1 mg. daily. [This dose is only half the amount found necessary for maintenance by Stresemann (*Lancet*, 1959, 2, 257). The very low maintenance dose of triamcinolone used by the authors (4.3 mg. daily) suggests that their patients did not suffer from severe chronic asthma, for which an average daily maintenance dose of 8 mg. of triamcinolone is required.]

H. Herxheimer

862. Death from Bronchial Asthma. [In English]

D. A. WILLIAMS and J. G. LEOPOLD. *Acta allergologica [Acta allerg. (Kbh.)]* 14, 83-86, 1959. 1 ref.

In this paper from St. David's Hospital, Cardiff, an analysis is presented of 101 deaths from status asthmaticus. Of the 101 patients, 69 were females; the authors state that there was a preponderance of females in each decade. Approximately 60 of the patients had had asthma for 10 years or longer, but some 20 in whom asthma developed in middle age died from the disease within a few years. Material obtained at necropsy in 25 cases and examined microscopically showed a cellular reaction in the bronchi and bronchioles with eosinophils, lymphocytes, and plasma cells. Neutrophils were often absent. The cellular reaction was maximal in the medium to small bronchi, but was absent in the respiratory bronchioles. In the authors' view the findings suggest that destructive emphysema does not occur in asthma uncomplicated by infective bronchitis. The most characteristic finding at necropsy in cases of active asthma is a widespread plugging of the bronchi with a thick gelatinous mucus containing eosinophil cells.

A. W. Frankland

Nutrition and Metabolism

863. Gluten-induced Enteropathy: the Effect of Partially Digested Gluten

A. C. FRAZER, R. F. FLETCHER, C. A. C. ROSS, B. SHAW, H. G. SAMMONS, and R. SCHNEIDER. *Lancet* [Lancet] 2, 252-255, Sept. 5, 1959. 4 figs., 17 refs.

In order to discover what components of gluten are responsible for the production of steatorrhoea in gluten-sensitive patients wheat gluten (untreated by "improvers") was digested first with pepsin at pH 1.8 and then with trypsin at pH 7.8, in each case for 4 hours at 37° C. The product was adjusted to pH 4.5 and an insoluble precipitate (Fraction VI) removed. The water-soluble material (Fraction III) yielded another water-soluble material (Fraction IIIA) when autoclaved at 120° C. for 20 minutes and two further fractions (IV and V) when dialysed against water at 4° C. Fraction III was antigenic when tested against gluten-sensitized guinea-pigs, but not Fraction IIIA.

The different fractions were then administered to 5 children and one adult suffering from proved gluten-sensitive steatorrhoea while they were free from steatorrhoea on a gluten-free diet. A positive response (steatorrhoea or clinical deterioration) occurred in one patient receiving Fraction III, in 3 receiving Fraction IIIA, and in one receiving Fraction IV and V combined (equivalent to Fraction III). No effect was produced in another patient by Fraction VI.

These results show that the toxicity of gluten is unrelated to any pretreatment of flour by improvers and throw doubt on the role of antigenicity in gluten sensitivity, as Fractions III and IIIA were equally effective in inducing steatorrhoea.

M. Lubran

864. Dietary Fats and the Diurnal Serum Triglyceride Levels in Man

P. T. KUO and J. C. CARSON. *Journal of Clinical Investigation* [J. clin. Invest.] 38, 1384-1393, Aug., 1959. 6 figs., 31 refs.

At the Hospital of the University of Pennsylvania, Philadelphia, the serum triglyceride, phospholipid, and cholesterol levels were measured hourly for 24 hours in 10 subjects with various serum lipid concentrations after stabilization on different diets, each diet being given until the fasting serum lipid level was constant before the test was performed. The diets used were (a) a high-animal-fat diet (100 to 140 g.), (b) an isocaloric low-fat diet, and (c) a corn-oil diet (120 to 160 g. fat, constituting 50 to 70% of the total caloric intake).

In all subjects the diurnal variations in serum phospholipid and cholesterol concentrations were small, although their levels varied with the different diets. The diurnal variation in the serum triglyceride level was small on the low-fat diet, but on the other two diets the level rose appreciably after meals, the animal-fat diet producing a greater and longer lasting rise than the corn-oil diet. This effect was marked in 4 normal subjects and 2 with

pure hypercholesterolaemia (without hyperlipaemia), but slight in 4 with hyperlipaemia. The change from the high-animal-fat to the low-fat diet resulted in a significant increase in the fasting serum triglyceride level in the hyperlipaemic subjects, but only a small increase in the normal and hypercholesterolaemic subjects.

M. Lubran

865. Further Observations on Postgastrectomy Steatorrhoea: the Effect of High Carbohydrate Intake and of Hydrochloric Acid Administration on Fat Absorption

P. VANAMEE, W. LAWRENCE JR., S. LEVIN, A. S. PETERSON, and H. T. RANDALL. *Annals of Surgery* [Ann. Surg.] 150, 517-527, Sept., 1959. 5 figs., 22 refs.

A defect in the absorption of fat is frequently involved in the impairment of nutrition which may develop in patients after gastrectomy. In a study at the Sloan-Kettering Institute, New York, of the possible relationship in such cases between the absorption of fat and the quantity of carbohydrate ingested 28 patients were given a diet containing a low proportion of carbohydrate and moderate proportions of fat and protein; after a 3-day adjustment period on this diet metabolic collections were analysed for 3 days (control period), after which the carbohydrate intake was doubled while the fat intake was kept constant and further balance studies carried out. Of the 28 patients, 14 had undergone subtotal gastrectomy (with pancreatectomy in 2 cases) and 14 total gastrectomy; a further 4 patients who had no known gastro-intestinal disease were included and served as controls. Defective fat absorption was defined as absorption of 92% or less of ingested fat.

It was shown that the absorption of fat was decreased in 13 out of 27 of the gastrectomized patients after changing to the high-carbohydrate diet, the decrease ranging from 5% to 54% of control values; 7 of these 13 patients had shown defective absorption of fat during the control period. In the remaining 14 patients, 6 of whom had defective absorption of fat during the control period, fat absorption was not further decreased after changing to the high-carbohydrate diet. The effect of administration of 25 ml. of 0.1N hydrochloric acid 5 minutes before each of the three main meals was then studied in 13 of the patients who had shown either a defect in fat absorption initially or in whom a defect could be created by a high carbohydrate diet. As a result of this therapy 5 patients were brought into the normal range of fat absorption and 4 others showed marked improvement in absorption.

The reason for these findings is not fully understood. It is recalled that a high carbohydrate intake is known to produce dumping symptoms in many gastrectomized patients and this study confirms that in many patients also it has the disadvantage of decreasing the absorption of fat. It has also been observed that some improvement of the defect in fat absorption occurs with increase in the length of time since operation.

Joseph Parness

Gastroenterology

866. Some Experiments on Partially Purified Gastrointestinal Mucosubstance

N. G. HEATLEY. *Gastroenterology* [*Gastroenterology*] 37, 304-312, Sept., 1959. 3 figs., 8 refs.

In experiments carried out at the Sir William Dunn School of Pathology, Oxford University, it was found that if the viscous secretions from the pylorus and duodenum of the pig were passed through a sintered glass filter a mucosubstance was retained on the filter which contained at least two molecular species. This substance, which could be washed, was found to have a fibrous character and to differ from mucin when taken up in physiological saline or other electrolytes. Discussing the character of this mucosubstance the author states that its viscosity is nearly all associated with its gross structure and is very sensitive to even gentle handling. The material is a mucoprotein the physical properties of which are strongly dependent upon pH and on the presence or absence of electrolytes. The buffering power of this mucoprotein is slight and the amount normally present in 100 ml. of pyloric secretion would not naturally neutralize more than about 0.3 ml. of N/10 hydrochloric acid.

Thomas Hunt

867. Mucosubstance as a Barrier to Diffusion

N. G. HEATLEY. *Gastroenterology* [*Gastroenterology*] 37, 313-317, Sept., 1959. 4 figs., 7 refs.

The concentration of mucosubstance in the pyloric secretion of pigs is seldom greater than 0.1%. When separated as a film on a sintered glass filter [see Abstract 866] it does not appear to hold back pepsin or pepsinogen, thus making virtually no difference to the rate of diffusion of the pepsin through the filter. Mucin itself has little buffering power and does not inhibit the action of pepsin. Its protective action in the stomach is thought to depend upon the fact that it can slow down gross mixing by its viscous gel-like qualities, thus acting as a barrier between the mucosa and the acid or pepsin in the stomach. The mucus layer is flexible and can swell greatly; it is constantly renewed and is most highly concentrated on the mucosal side and least on the luminal side. It has a very high viscosity, and this and other physical qualities will vary with the pH. There will be a pH gradient through the mucous layer, which should therefore be regarded rather as a dynamically maintained barrier almost of a multilayer nature than as a mere static membrane of constant thickness and character.

Thomas Hunt

868. The Management of Recurrent Aphthous Stomatitis

W. SIRCUS. *British Medical Journal* [*Brit. med. J.*] 2, 804-806, Oct. 24, 1959. 3 refs.

In a previous paper (*Quart. J. Med.*, 1957, 26, 235; *Abstr. Wld Med.*, 1957, 22, 356) the author drew attention to the many different remedies which have been tried in

the management of recurrent aphthous stomatitis. He now describes a treatment trial by the double-blind technique which was carried out on 13 consecutive patients at the Western General Hospital, Edinburgh, in whom aphthous ulcers were present continuously or with very brief remissions. The mean age of the patients (9 female and 4 male) was 39 years (range 28 to 60 years). In 3 cases the disorder was familial. The plan of treatment was as follows. One month after an initial consultation and examination each patient was given lozenges of identical appearance and taste containing respectively: (a) a dummy preparation without any active ingredients, (b) 10 mg. of framycetin sulphate ("soframycin"), and (c) a combination of 10 mg. of framycetin sulphate and 1 mg. of prednisolone, the sequence of distribution of the different lozenges being by random selection. Each preparation was taken in doses of 6 lozenges daily for 28 days, the lozenges being dissolved slowly in the mouth. At the end of the 3-month double-blind trial 11 of the patients received linguets containing 2.5 mg. of hydrocortisone hemisuccinate 6 times daily for 28 days and 8 patients received tablets containing 0.75 gr. (50 mg.) of quinalbarbitone sodium twice daily for a further period of 28 days; this part of the trial was open.

Analysis of the results as assessed from the diary entries of each patient showed that 4 patients responded equally well during every phase of the trial, including the period on dummy lozenges; 3 of these also responded well during the period following the initial consultation. In 3 patients there was improvement in the period immediately after the consultation, followed later by a relapse after which there was no response to any form of therapy, while a further 3 patients did not respond to either the consultation or any form of treatment. The remaining 3 patients in the series responded only to steroids as shown by the satisfactory results obtained with the steroid combined with the antibiotic or the steroid alone and the lack of response to the antibiotic alone. Thus treatment with lozenges containing a steroid was the most useful of the methods examined.

It is noted that only 4 patients were considered to have a stable social background and a normal, fully adjusted personality. The evidence from this and the previous study indicates that suggestion and medical interest play an important part in the control of these cases, especially those in which chronic anxiety, tension, or depression of exogenous origin is present.

Joseph Parness

869. Enlargement and Round Cell Infiltration of the Salivary Glands Associated with Systemic Disease

P. H. FUTCHER. *Bulletin of the Johns Hopkins Hospital* [*Bull. Johns Hopk. Hosp.*] 105, 97-107, Sept., 1959. 1 fig., 38 refs.

A series of 10 carefully selected cases of salivary-gland enlargement of unusual aetiology seen at the Johns Hopkins Hospital, Baltimore, is reported, cases in

which the enlargement was due to more usual causes, such as mumps, pyogenic infection, calculi, sarcoidosis, dehydration and malnutrition, diabetes, and liver disease having been excluded. In all 10 patients (females over 40 years of age) there was obvious evidence of associated systemic disease. Joint pains, disorders of the eyes, glandular enlargement, splenomegaly, and purpura were common. Hyperglobulinaemia was present in 5 out of 9 patients, and in 6 the leucocyte count on at least one occasion was 4,500 per c.mm. or less. A raised erythrocyte sedimentation rate "was the rule". Histological examination of salivary gland tissue from 8 patients showed lymphoid hyperplasia and infiltration and loss of acini. Systemic lupus erythematosus was diagnosed in 3 cases, scleroderma in one, and rheumatoid arthritis in one.

It is emphasized that a careful search should be made for evidence of other systemic manifestations in patients with enlargement of the salivary glands not due to the more usual causes.

John Fry

STOMACH AND DUODENUM

870. Studies of Local Gastric Cooling as Related to Peptic Ulcer

O. H. WANGENSTEEN, P. A. SALMON, W. O. GRIFFEN JR., J. R. S. PATERSON, and F. FATTAH. *Annals of Surgery* [Ann. Surg.] 150, 346-358, Sept., 1959. 5 figs., 7 refs.

This paper from the University of Minnesota Hospital, Minneapolis, presents a further report on the effects of intragastric cooling in the treatment of massive gastro-duodenal haemorrhage. In preliminary studies on various species of laboratory animals an intragastric balloon was used, and cooling down to 10° to 14° C. was shown to inhibit the quantity and quality of the gastric secretions and reduce the rate of blood flow in the stomach. Attempts were then made to produce intragastric cooling in these animals without the intermediary of a balloon. The two main problems to be overcome were the prevention of oesophageal reflux and the choice of a suitable perfusing fluid. Neither problem has been entirely satisfactorily solved, but suitably treated and buffered milk was found to meet most of the requirements.

In a clinical trial 30 patients with massive gastro-duodenal or oesophageal haemorrhage were then treated by intragastric cooling. In 11 of these who had duodenal ulcer prompt and permanent cessation of the bleeding occurred within 6 hours. In 3 others, in whom the bleeding was acute in nature and followed a period of marked stress or prolonged steroid therapy, the bleeding recurred. However, 2 cases of bleeding from benign gastric ulcer were successfully controlled, while of 5 patients with bleeding from oesophageal varices the haemorrhage was controlled for sufficient time in 4 to prepare for definitive surgery; it is pointed out that in 4 of these cases use of the Sengstaken-Blakemore tube had failed to control the bleeding. Although the bleeding was at first controlled in 2 cases of haemorrhagic gastritis, it recurred in both and operation became necessary. The method was also used with partial suc-

cess in some cases of postoperative bleeding and bleeding due to disseminated carcinoma, though many of these cases were not ideally suitable for the treatment. The authors' technique is only briefly outlined in this paper, having been fully described in two previous papers (*Surgery*, 1958, 44, 265, and *J. Amer. med. Ass.*, 1959, 169, 1601). Finally [and provocatively] it is suggested that the technique might be used in combination with other measures to accelerate the healing of peptic ulcers. The resultant general body cooling is prevented by the use of suitably heated blankets.

[It is impossible in an abstract to do full justice to the brilliance of this research work.]

Andrew M. Desmond

871. Early Diagnosis of the Causes of Haematemesis

G. N. CHANDLER and G. WATKINSON. *Quarterly Journal of Medicine* [Quart. J. Med.] 28, 371-395, July [received Sept.], 1959. 13 figs., bibliography.

The authors, working at the General Infirmary at Leeds and St. James's Hospital, Leeds, studied 238 patients admitted consecutively as an emergency for haematemesis or melaena, or both, by hourly gastric aspiration through an indwelling Ryle's tube. Their object was to observe the value of aspiration in the management of such cases and to study changes in the pH of the aspirated stomach contents as measured by means of a glass electrode.

Blood-staining of some or all of the aspirates occurred in 28 of 40 cases of chronic gastric ulcer, but in only 34 of 76 patients with duodenal ulcer. Continued melaena with early clearing of the gastric aspirate was suggestive of duodenal ulcer. The recurrence of staining by fresh blood gave warning of renewed haemorrhage in 10 of 11 cases of chronic gastric ulcer and 10 of 12 cases of acute gastric ulcer, but in only 3 of 14 cases of chronic duodenal ulcer. In a further 24 patients the recurrence of blood in the aspirate was not followed by other evidence of renewed bleeding.

Of those patients with peptic ulceration, 33 showed normal acidity of the aspirated gastric contents, the pH being between 2.0 and 4.5. This was of no diagnostic significance. Of 33 patients showing nocturnal neutralization, the values in 2 cases being more alkaline than pH 5.5, 26 had chronic gastric ulcer. Of 68 patients with high night acidity, 7 of them with values below pH 2.0, 57 had chronic duodenal ulcer. Of 78 patients with achlorhydria, no values being below pH 3.5, 69 had acute lesions.

The achlorhydria of acute peptic ulcer could not be attributed entirely to neutralization of the stomach contents by blood, since experiments showed this effect to be very short-lived and achlorhydria was present as frequently in the absence of blood-staining as in its presence. It is suggested that it results from a combination of shock and an underlying acute gastritis or chronic reduction in the number of parietal cells. Gastroscopy was undertaken during the first week after admission on 24 patients in whom a diagnosis of acute ulcer was ultimately made. The gastroscopic appearance of superficial gastritis was seen in 14 patients, of whom 5 also showed

areas of chronic atrophic gastritis. Mucosal erosions or subacute ulcers, or both, were seen in 16 patients. The achlorhydria of acute ulcer was short-lived in those patients on whom subsequent tests were made unless gastroscopic evidence of an atrophic process had been found.

The authors recommend the use of hourly diagnostic gastric aspiration and determination of the pH for at least 24 hours, and if possible for 12 hours after bleeding has stopped, in the routine management of patients with haematemesis.

G. L. Asherson

LIVER AND GALL-BLADDER

872. Splenic Pulp Manometry as an Emergency Test in the Differential Diagnosis of Acute Upper Gastrointestinal Bleeding

W. F. PANKE, L. M. ROUSSELOT, and A. H. MORENO. *Surgery, Gynecology and Obstetrics* [Surg. Gynec. Obstet.] 109, 270-278, Sept., 1959. 2 figs., 6 refs.

The authors state that in the U.S.A. approximately 25% of cases of acute bleeding from the upper gastrointestinal tract are due to oesophageal varices. There is therefore a great need for a method which will readily distinguish this condition from other causes of bleeding; in particular, since peptic ulcer occurs with greater frequency in patients with hepatic cirrhosis, it is desirable to know which of the two conditions is the source of the haemorrhage. The authors have previously shown (*Surg. Clin. N. Amer.*, 1958, 38, 421) that a high pressure within the splenic pulp is almost invariably associated with oesophageal varices, as demonstrated by portal venography. In the present paper they endeavour to show that percutaneous splenic pulp manometry alone is a sufficient guide to the presence of varices.

The method, which was fully described in the paper cited, is simple, requires no complex apparatus, and has a low morbidity. It was used in the examination of 113 patients who had suffered severe bleeding from the upper alimentary tract and in whom the diagnosis was subsequently confirmed either by laparotomy or radiology and portal venography. The mean splenic pulp pressure of patients who had bled from varices was consistently higher (413 mm. H₂O) than in those who had bled from other causes (175 mm. H₂O). It was further shown that all patients in whom the pressure was above 290 mm. H₂O were bleeding from varices, while all with a pressure below 250 mm. H₂O were bleeding from other causes. It is stated that the small region of overlap does not cause much trouble in practice; in the present series only 11 patients (about 10%) fell within the range 250 to 290 mm. H₂O, of whom 4 were bleeding from varices. Furthermore any patients with bleeding varices and a splenic pulp pressure in this indeterminate range stop bleeding quickly with conservative means. Thus in this series the method was accurate in 90% of cases; and not only did it detect portal hypertension when this was clinically unsuspected, but it also indicated bleeding from sources other than oesophageal varices in known cirrhotic patients.

A. G. Parks

873. Thromboplastin Generation as a Test of Liver Function

S. F. RABINER and T. H. SPAET. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 238, 280-286, Sept., 1959. 4 figs., 13 refs.

The serum thromboplastin generation test (S.T.G.T.), which will detect deficiency in the serum of the clotting Factor X, was carried out at the New York Hospital, Cornell Medical Center, and the Montefiore Hospital, New York, on normal subjects, patients with proved liver disease, and patients with recent hepatitis or hepatic enlargement in whom all liver function tests gave negative results. The clotting time was greater than in the control group in 23 out of 33 cases of known liver disease and in 9 out of 17 of suspected liver disease. There was no deficiency of plasma thromboplastin component in any patient.

Aged serum is also deficient in Factor X. This deficiency was corrected by serum from 17 out of 18 normal subjects, but was not corrected by serum from 18 out of 22 patients with known liver disease and 6 out of 12 patients with suspected liver disease. None of the sera with which the S.T.G.T. gave an abnormal result could completely correct the deficiency in aged serum. The prothrombin time was normal in most cases and was not correlated with result of the S.T.G.T. The test appears to provide a useful index of liver function.

M. Lubran

874. Lateral Portacaval Anastomosis for Portal Hypertension: Long Term Results in 58 Patients with Intrahepatic Portal Bed Block and 7 Patients with Extrahepatic Portal Bed Block

T. B. PATTON, C. G. JOHNSTON, C. LYONS, and P. JORDAN JR. *American Journal of Gastroenterology* [Amer. J. Gastroent.] 32, 291-308, Sept., 1959. 5 figs., 43 refs.

The authors have analysed carefully the results of 70 operations for the performance of lateral portacaval anastomosis on 65 patients at various hospitals in the U.S.A. during the past 10 years and present the results in 16 tables. [The article is in itself a summary and only a few of its more important features can be considered here.]

The age range of the 57 patients undergoing operation for intrahepatic block was 11 to 70 years and of the 8 treated for extrahepatic block 5 months to 42 years. Haematemesis was the usual presenting complaint. Whenever possible tamponade was used to control the bleeding of oesophageal varices, but if bleeding persisted for 12 to 24 hours after tamponade was instituted trans-thoracic or transabdominal transoesophageal ligation of varices was carried out, the thoracic route being preferred when vascular adhesions were likely to be present. When the obstruction was intrahepatic the standard lateral portacaval anastomosis was carried out, the portal vein being anastomosed to the inferior vena cava, an important procedure being the removal of an ellipse of tissue from the walls of both vessels to prevent closure of the shunt. The pressure in the portal vein was recorded before and after the formation of the shunt. The operation used for more mature patients with extra-

hepatic obstruction was splenorenal anastomosis, but this type of shunt does not remain patent in young children, in whom it is recommended that a portacaval shunt be performed or repeated ligation of oesophageal varices carried out until the patient is over 10 years old, when splenorenal anastomosis can be performed.

In this series of cases there were 11 deaths within 30 days, 8 of which were directly attributable to liver disease rather than to the operation. Between 41 days and 91 months there were 19 deaths, only 9 being directly attributable to the liver condition. All these deaths were in the group with intrahepatic obstruction. Development of hepatic coma proved a problem in cirrhotics, especially those who were also alcoholics. Liver function tests were carried out before and after treatment on 14 patients with intrahepatic obstruction, but the operation produced no marked improvement.

The main advantage of the lateral portacaval shunt over the Eck fistula and splenorenal shunt is that of technical simplicity, but in addition late closure of a splenorenal shunt is relatively common and the spleen has to be removed. However, all forms of shunt operation divert blood from the liver and so probably lessen parenchymal regeneration. *W. H. Horner Andrews*

875. A Clarification of Some Hemodynamic Changes in Cirrhosis and Their Surgical Significance

W. D. WARREN and W. H. MULLER JR. *Annals of Surgery* [Ann. Surg.] 150, 413-427, Sept., 1959. 8 figs., 24 refs.

At the University of Virginia Hospital, Charlottesville, portal pressure was determined before side-to-side portacaval shunt, immediately after operation, and again after an interval in 8 patients with oesophageal varices due to hepatic cirrhosis. From the findings the authors conclude that the site of obstruction in cirrhosis is between the sinusoids and the hepatic veins. With increasing obstruction the flow of blood from the liver may be reversed and may be via the portal vein. They consider, therefore, that the operation of choice in portal hypertension due to cirrhosis is a side-to-side and not an end-to-side portacaval shunt.

[This interesting paper should be read in full as the methods of investigation and full results are not suitable for abstracting.] *B. F. Swynnerton*

876. The Treatment of Ascites by Side to Side Portacaval Shunt

C. S. WELCH, H. F. WELCH, and J. H. CARTER. *Annals of Surgery* [Ann. Surg.] 150, 428-440, Sept., 1959. 5 figs., 23 refs.

After discussing present views on the mechanism responsible for the formation of ascites in hepatic cirrhosis the authors describe the results obtained with side-to-side portacaval shunt for the relief of ascites in 14 patients, 13 of whom had alcoholic cirrhosis. There were 3 operative deaths, 2 of them from liver failure, and 4 late deaths from liver failure (4 to 22 months after operation). Ascites reaccumulated in only one of these patients. The remaining 7 patients were free from ascites 3 to 26 months after operation. It is pointed out that before

operation the ascites was difficult to control and liver function, as measured by the serum albumin concentration and "bromsulphalein" excretion, was in general worse than in patients with oesophageal varices who would be considered reasonable operative risks. After operation the results of liver function tests tended to improve.

In the authors' view operative treatment of ascites should not be undertaken "lightly or haphazardly". Further studies designed to determine the type of patient most likely to benefit and the contraindications are contemplated. *B. F. Swynnerton*

INTESTINES

877. The Articular Manifestations of Chronic Ulcerative Colitis

L. FERNANDEZ-HERLIHY. *New England Journal of Medicine* [New Engl. J. Med.] 261, 259-263, Aug. 6, 1959. 1 fig., 18 refs.

Examination of the records of 555 patients, 265 (47.7%) of them male, treated at the Lahey Clinic between 1926 and 1955 for chronic ulcerative colitis revealed that articular manifestations occurred in 95 (17%) of these patients, of whom 41 were male. These manifestations were of 5 types: (1) rheumatoid spondylitis occurred in 28 patients (5%), 20 of them being male. In 5 patients symptoms of the spondylitis were encountered before the onset of colitis, but in 15 they were reported afterwards. In only 4 cases was there any correlation between the spondylitic symptoms and the colitis. Colectomy and ileostomy were performed on 15 patients, but the rheumatoid spondylitis progressed postoperatively in 12. (2) Arthralgia of the peripheral joints occurred in 23 patients (4.2%), 7 male, having preceded the colitis in 5 cases and followed it in 10. In 20 cases the arthralgia ran a parallel course to the colitis. Colectomy and ileostomy were performed on 15 of these patients, of whom only one complained of arthralgia postoperatively. (3) Rheumatoid arthritis appeared in 18 patients (3.2%), 7 male, preceding the colitis in only one case and following it in 14. In only 8 patients did the activity of the arthritis parallel the ebb and flow of the colitis. Colectomy and ileostomy were carried out on 11 patients, but the arthritis progressed postoperatively in 10. (4) Lesions of erythema nodosum were noted in 16 patients (2.8%), 3 of them male, and was associated with arthralgia or acute arthritis in all the cases. The erythema nodosum preceded the colitis in only 2 cases, appeared simultaneously in 7, and occurred afterwards in 7; in 14 cases the activity of the 2 conditions ran a parallel course. None of the 9 patients who underwent colectomy and ileostomy suffered a postoperative recurrence of the lesions. (5) The final group of 10 patients (1.8%), of whom 4 were men, had articular manifestations which could not be included in any of the previous categories and are referred to as "acute toxic arthritis". In all cases there was swelling which affected the large joints only, this occurring simultaneously with the first attack of colitis in 6 cases and with subsequent attacks

in 3; in one it occurred before the colitis. The articular manifestations were completely absent during periods of quiescence of the colitis. All these patients underwent colectomy and ileostomy, but in none did the articular manifestations recur postoperatively.

It is concluded that there is no close association between the courses of rheumatoid spondylitis and chronic colitis nor between those of rheumatoid arthritis and colitis. In neither case is the arthritis an indication for colectomy. In the other three groups the course more closely paralleled that of the arthritis, but except possibly in some of the miscellaneous conditions the symptoms were not severe enough to justify colectomy unless other reasons were present. In conclusion the author agrees with Bergen, who stated in 1939 that "whether or not the arthritis should be called a complication or an associated disease is a debatable question".

J. Warwick Buckler

878. Toxic Megacolon in Ulcerative Colitis

J. L. A. ROTH, A. VALDES-DAPENA, G. N. STEIN, and H. L. BOCKUS. *Gastroenterology* [Gastroenterology] 37, 239-255, Sept., 1959. 8 figs., 8 refs.

Toxic megacolon is described as extreme dilatation of a segment or of the whole of an inflamed colon, and may occur in a fulminating first attack or in the course of an acute relapse of chronic ulcerative colitis. The authors describe 15 such attacks in 12 patients with this disease seen at the Graduate Hospital, University of Pennsylvania, Philadelphia, between 1945 and 1958, of which 9 occurred during acute fulminating episodes in 6 patients with the relapse-remitting type of colitis; in 5 patients toxic megacolon complicated primary fulminating disease and in one patient it developed during an acute relapse of chronic disease.

Clinically these patients were very ill, with high fever, tachycardia, leucocytosis, and listlessness or other mental disturbance. The abdomen was tender and markedly distended, suggestive of colonic obstruction, while bowel sounds were usually diminished and feeble. Perforation of the colon, virtually "silent", occurred in some cases. Nutritional deficiencies soon followed and the haemoglobin value and serum albumin and prothrombin levels fell. Low serum sodium and chloride levels were common but, surprisingly, serum potassium levels were usually unaltered. Aerophagy was a prominent feature in 7 patients, producing hiccup and gastric distension, and may have played an important part in the production of the megacolon. Other complications of ulcerative colitis, such as perforation of the colon and thrombophlebitis, were more common than in simple fulminating disease. Radiology demonstrated that the gaseous distension of megacolon was often localized, but invariably the transverse colon was most seriously affected. In 3 cases the whole colon was distended. The attacks lasted from 8 days to 2 months, 9 of them being ended abruptly, by surgery in 3 cases, by ACTH in 2, spontaneously in 3, and by death in one; the others ended gradually, 3 doing so spontaneously. The role played by steroids was not clear; thus 2 attacks of megacolon developed while the patient was being treated with ACTH, while of the 5 attacks treated by

steroid therapy, 3 improved. Of 6 patients treated surgically, 2 died in the postoperative period and the colons of these patients were studied post mortem. The wall was very thin and in 2 cases (or possibly 3) had perforated. There was marked damage to the muscle layers, with active diffuse inflammation and marked capillary proliferation, especially in the inner layer. In 3 cases there was considerable leucocytic infiltration of the myenteric neuroplexuses. In 2 cases the most severe changes were found in segments distant from the dilated segment.

The authors conclude that many factors are responsible for the production of megacolon in ulcerative colitis, including especially the inflammatory damage to muscles and nerves, the aerophagy, and possibly slight stenosis of the colon distally.

A. Gordon Beckett

879. Serum Proteins in Ulcerative Colitis. I. Electrophoretic Patterns in Active Disease

R. O. BICKS, J. B. KIRSNER, and W. L. PALMER. *Gastroenterology* [Gastroenterology] 37, 256-262, Sept., 1959. 4 figs., 41 refs.

In this study reported from the University of Chicago electrophoresis revealed abnormal serum protein patterns in 61 out of 63 patients with active ulcerative colitis, 16 of them showing a low serum albumin level and an increase in α_2 globulin, while the other 45 showed these changes together with hypergammaglobulinaemia; a fast-moving γ_1 or "T" globulin was observed in 4 cases. The authors regard the increase in α_2 globulin as non-specific evidence of activity and the low albumin level as evidence of protein from the bowel. As similar changes in the γ globulins are seen in such diseases as myeloma, rheumatoid arthritis, and rheumatic fever they suggest that in ulcerative colitis the high γ -globulin level is evidence of increased antibody production.

A. Gordon Beckett

880. Serum Proteins in Ulcerative Colitis. II. The Effects of Therapy Correlated with Electrophoretic Patterns

R. O. BICKS, J. B. KIRSNER, and W. L. PALMER. *Gastroenterology* [Gastroenterology] 37, 263-267, Sept., 1959. 21 refs.

The authors have studied the improvement in the abnormal serum protein patterns in ulcerative colitis previously reported [see Abstract 879] as a result of treatment with ACTH or adrenal corticosteroids. Of the 45 patients with increased γ -globulin levels, 35 responded very well clinically to the steroids, there being a slow fall in the γ -globulin level, which was maintained so long as the disease was controlled. In contrast, only 3 of the 16 patients without hypergammaglobulinaemia responded well, no changes in the α_2 -globulin level being observed; variations in the albumin fraction reflected improvement in the nutritional status of the patient.

The authors conclude that the steroids are most effective in patients with high γ -globulin concentrations and that they either suppress antibody synthesis or suppress its effects.

A. Gordon Beckett

Cardiovascular System

881. Some Methodologic Problems in the Long-term Study of Cardiovascular Disease: Observations on the Framingham Study

T. GORDON, F. E. MOORE, D. SHURTLEFF, and T. R. DAWBER. *Journal of Chronic Diseases* [*J. chron. Dis.*] 10, 186-206, Sept., 1959. 11 refs.

This is the fourth of a series of reports on what has become known as the Framingham survey—a long-term inquiry into the epidemiology of atherosclerotic and hypertensive cardiovascular disease started in 1948 by the U.S. National Heart Institute. The inquiry was prospective, the broad plan being to examine medically a population aged 30 to 60 years—the age range in which these diseases are known to develop—and to re-examine at 2-year intervals over a long period those persons found initially to be free from the diseases concerned. During surveillance two groups would emerge—one consisting of those who developed the diseases and the other of those who remained free. It was hoped that comparison of the records of the two groups would point to aetiological factors.

The considerations which led to the town of Framingham, Massachusetts, being selected for the study are restated. A random sample consisting of 2 out of every 3 families was selected and approximately 6,500 persons aged 30 to 59 years were invited to take part. But although there were reasons to expect good cooperation and in spite of heavy propaganda and the extension of the intake period from one to 4 years the response from this sample was only 69% (4,469). The conclusion is drawn "that community studies of chronic disease which require clinic visits are not likely to have a high level of participation". To augment the numbers 740 volunteers—residents not included in the original sample—were accepted into the survey, their experience being analysed separately. Subsequent losses during follow-up to the fourth examination [presumably the sixth anniversary of date of entry] reduced the number in the respondent group from 4,469 to 3,843 (86%) and in the volunteer group from 740 to 698 (94%).

The present report is mainly concerned with the assessment of possible biases introduced by the deficiency in the initial response and by the subsequent losses. Evidence is presented [which should be consulted in the original] to indicate that the non-respondent group was overweighted with unhealthy and the respondent group with healthy persons. For example, mortality in 1951 and 1952 amongst non-respondents was double that in the respondent group—and in men, but not women, this was equally evident for both cardiovascular and non-cardiovascular deaths. This bias would have been important if the object of the survey had been to measure inception or prevalence rates of cardiovascular disease, but since the original plan was to follow up only those free from such disease (although later it was decided to

keep all persons under observation) the amount of bias introduced is considered of little import. The subsequent losses were variously due to death (3%), refusal (7%), and removal (4%). Certain characteristics of these three categories are defined, but the conclusion reached is that for the prospective evaluation of hypotheses the biases introduced by losses of these dimensions are trivial.

Some results of the survey to date are of interest to other workers in this field. There was no evidence that the serum cholesterol level changed after recovery from a coronary thrombosis. For 84 men the mean value at the examination before the event was 243.5 mg. per 100 ml. compared with 246.3 mg. per 100 ml. at the first examination after the event, and the corresponding values for 33 women were 276.8 and 278.8 mg. per 100 ml. Blood pressure and relative weight also remained materially unchanged. Among men who developed coronary heart disease no real difference in weight, blood pressure, or serum cholesterol level could be demonstrated as between those who died shortly after the clinical manifestation of the disease and those surviving longer. But of 61 women who developed the disease, the 8 who died weighed less, but had higher serum cholesterol levels, than those surviving at the fourth examination.

[Various pitfalls in planning such surveys may be avoided by studying the lessons which the authors point from their experience in this investigation, which has extended over more than 10 years.] E. Lewis-Fanning

882. Effect of Mitral Valvulotomy on Tricuspid Insufficiency Associated with Mitral Stenosis

P. F. ANGELINO, B. LO BUE, and V. LEVI. *Circulation* [*Circulation*] 20, 360-366, Sept., 1959. 3 figs., 17 refs.

This report from the Institutes of Pathology and Heart Surgery, University of Turin, analyses the results of mitral valvotomy in 20 patients who had tricuspid insufficiency as well as mitral valvular disease. In 13 cases the mitral lesion was a pure stenosis; of these patients, 3 did well, losing the signs of tricuspid insufficiency, 3 derived some benefit although the tricuspid insufficiency was little changed, but the other 7 did badly, apparently because of irreversible pulmonary vascular disease. In the remaining 7 of the 20 cases there was significant mitral regurgitation, bad enough to justify an attempt at plastic repair of the mitral valve in 2 of them, but all did badly.

Thus it is concluded that in the presence of tricuspid insufficiency only patients with pure mitral stenosis should be considered for surgery, and those likely to have irreversible pulmonary vascular changes should be rejected. The authors have found that intravenous reserpine is a useful agent in distinguishing between "anatomical" and "functional" pulmonary arterial

resistance, and described its use in detail in an earlier paper (*Minerva cardiologia*. (Torino), 1956, 4, 165).

J. A. Cosh

883. The Effect of Calcium Chelation on Cardiac Arrhythmias and Conduction Disturbances

S. JICK and R. KARSH. *American Journal of Cardiology* [Amer. J. Cardiol.] 4, 287-293, Sept., 1959. 3 figs., 18 refs.

The chelating agent sodium calciumedetate ("sodium versenate", NaEDTA), was given intravenously in a dose of 3 g. in 400 ml. in half an hour to 27 patients at the Jewish Hospital, St. Louis, suffering from abnormalities of rhythm or some other cardiac conduction defect. In 11 cases in which the arrhythmia was associated with digitalis intoxication the effect of NaEDTA was to produce a marked fall in the serum calcium level, without much change in that of potassium, and a reduction in the frequency of ventricular premature beats and the severity of the arrhythmia for periods of 15 minutes to 2 hours. In 16 patients with similar electrocardiographic abnormalities not associated with digitalis therapy there was less change in the serum calcium level and virtually no change in the electrocardiogram. The authors conclude that NaEDTA given by intravenous infusion may be of value as an emergency measure in cases of digitalis overdosage. J. Robertson Sinton

DIAGNOSTIC METHODS

884. The Clinical Uses of Oximetry

M. B. McILROY. *British Heart Journal* [Brit. Heart J.] 21, 293-314, July [received Sept.], 1959. 21 figs., 10 refs.

The clinical value of oximetry was studied at the Institute of Cardiology and the National Heart Hospital, London, in more than 300 patients, a single-scale ear oximeter calibrated against arterial blood samples analysed by Haldane's method being used to record changes in arterial oxygen saturation after Valsalva's manoeuvre, amyl nitrite inhalation, exercise, oxygen breathing, and changes in posture.

The author states that there is often a right-to-left shunt after Valsalva's manoeuvre in cases of atrial septal defect, due to rapid filling of the right atrium. This will cause a transient fall in oxygen saturation. If this fall does not occur after operation the defect has been adequately repaired. Shunt reversal at rest after the manoeuvre indicates a small defect, while shunt reversal only following exercise after the manoeuvre indicates a moderate defect. If the defect is large no shunt reversal occurs. In cases of Fallot's tetralogy the arterial oxygen saturation falls after exercise, after inhalation of amyl nitrite, or on rising from the squatting position. None of these changes occurs in simple pulmonary stenosis and the procedure is therefore useful in differential diagnosis. Cyanosis due to lung disease can be differentiated from that due to right-to-left shunts by allowing the patient to breathe pure oxygen. In lung disease there is a rapid exponential rise in oxygen saturation, while in cases of shunt there is a slower, linear rise.

From this linear rise a rough estimate can be made of systemic and pulmonary blood flow, the formula for which is given. Oximetry also contributes information which is helpful in the diagnosis of several cyanotic lesions, and the site of an intracardiac shunt in pulmonary hypertension can often be determined by this means.

D. Goldman

885. High Chest Leads and Minor Myocardial Infarctions

H. ROESLER. *British Heart Journal* [Brit. Heart J.] 21, 407-414, July [received Sept.], 1959. 5 figs., 26 refs.

The importance in the diagnosis of ischaemic heart disease of relatively minor electrocardiographic changes, together with the necessity of recording from chest leads at a higher level than usual, is indicated by this study of 9 patients seen at the Temple University Medical Center, Philadelphia. All but one of the patients had angina pectoris and 3 were diabetic.

In most of the patients three particular changes in the T wave were noted—it was lower in Lead I than in Lead III, negative in Lead aVL, and high in Lead aVF. In 5 patients T was normal in the left-sided chest leads taken at the usual level, but was abnormal when higher levels (level of 3rd rib) were employed, the abnormalities including low voltage, notching, and inversion. Only in one case were significant Q waves seen in the chest leads either at the normal or high level. In one case the QRS and T abnormalities indicating infarction high in the antero-lateral wall had mainly disappeared 17 months later.

The author emphasizes the importance of inversion of the T wave in diagnosing myocardial ischaemia when a history of angina is present. He concludes that the presence of the triad—T1 lower than T3, negative T in aVL, and high T in aVF—should always suggest infarction high in the antero-lateral wall, and it is in these patients particularly that high-level chest leads can provide significantly more information than the conventional precordial leads.

Gerald Sandler

CONGENITAL HEART DISEASE

886. Effects of Infusion of Acetylcholine on Pulmonary Vascular Resistance in Patients with Pulmonary Hypertension and Congenital Heart Disease

J. T. SHEPHERD, H. J. SEMLER, H. F. HELMHOLZ JR., and E. H. WOOD. *Circulation* [Circulation] 20, 381-390, Sept., 1959. 4 figs., 30 refs.

In this study, reported from the Mayo Clinic, pulmonary vascular resistance was measured by right heart catheterization in 11 patients ranging in age from 8 to 51 years who had pulmonary hypertension accompanying either atrial or ventricular septal defect. While continuous records were made of the pulmonary and systemic arterial pressures acetylcholine was infused into the pulmonary artery for a period of 1 to 2 minutes. The dose (usually 2 to 4 mg. per minute) was chosen individually for each patient, breathing air, so as to produce a pulmonary but not a systemic effect; sub-

sequently each patient's response was tested again while he breathed oxygen.

In six patients with an atrial septal defect an immediate fall in pulmonary arterial pressure and resistance followed the infusion of acetylcholine. The fall in pulmonary resistance averaged 23% of the resting value with acetylcholine alone, 29% on breathing oxygen alone, and 43% with oxygen and infusion of acetylcholine together. One patient with ventricular septal defect and one with both atrial and ventricular defects showed no response to the drug or to oxygen. The remaining 3 with ventricular septal defect showed a fall in resistance averaging 31% with acetylcholine alone, 33% with oxygen alone, and 57% with both together. From these results it is concluded that the high pulmonary vascular resistance in patients with these defects can be largely due to active vascular constriction of the pulmonary vessels.

J. A. Cosh

887. **Clinical Results of Correction under Hypothermia of Atrial Septal Defects and Pulmonary Valvular Stenosis** E. B. MAHONEY, J. A. MANNING, J. A. DEWEESE, and S. I. SCHWARTZ. *Journal of Thoracic and Cardiovascular Surgery* [J. thorac. cardiovasc. Surg.] 38, 292-308, Sept., 1959. 10 figs., 21 refs.

The authors, from the University of Rochester, New York, recount their experiences in the surgical correction under hypothermia of pulmonary valvular stenosis in 19 patients and of atrial septal defects of the ostium secundum type in 16.

Their operative technique varied little from previously described standard methods, with surface cooling to a rectal temperature of 32.5° C., but they have used coronary arterial perfusion during circulatory arrest in order to lessen the risk of ventricular fibrillation. [However, the incidence of this complication in their series does not seem to be much lower than in series in which this procedure was not employed.] The obstruction to the pulmonary outflow tract was in all cases at the valve, and this was divided in the usual way; there were no deaths in this group. The septal defects were sutured, and among these patients there was one operative death due to irreversible ventricular fibrillation. The authors discuss the importance of the obstruction to the right ventricular outflow by muscular hypertrophy; in none of their cases was such obstruction thought to be due to fibrosis, and although in many cases a gradient across the pulmonary valve persisted immediately after the performance of valvotomy, cardiac catheterization a year later showed that this gradient had disappeared in most cases, and that in more than half the cases the electrocardiogram had returned to normal.

J. R. Belcher

888. **Surgical Experiences in the Treatment of Congenital Mitral Stenosis and Mitral Insufficiency** G. W. B. STARKEY. *Journal of Thoracic and Cardiovascular Surgery* [J. thorac. cardiovasc. Surg.] 38, 336-352, Sept., 1959. 9 figs., 10 refs.

The author describes his experiences at the Children's Medical Center (Harvard Medical School), Boston, in the treatment of the rare cardiac anomaly of congenital

mitral valve disease occurring in 7 children aged 2½ to 15 years, in 5 of whom the valve was stenosed and in 2 it was incompetent. In all cases the diagnosis had been made in infancy, and none of the patients had a history of rheumatic fever. Of 4 of the 5 children with stenosis who were operated on by the closed method, one died 5 days after operation. The 5th child was operated on by the open method and also died. The 3 survivors, however, did well. Of the 2 patients with mitral incompetence, one was operated on by the open method and one by closed plication of the atrio-ventricular ring. In the first case there was some slight improvement, but in the second the result was excellent. It is pointed out that although 2 of these children died, all were gravely ill, and it is concluded that operative treatment for congenital disease of the mitral valve is well worth while.

J. R. Belcher

889. **Neuro-psychological Disorders in Cases of Congenital Cardiac Disease.** (Нервно-психические нарушения у больных врожденными пороками сердца) V. V. KOVALEV. *Журнал Невропатологии и Психиатрии* [Ž. Nevropat. Psihiat.] 59, 986-993, No. 8, 1959. 41 refs.

The author reports the principal neurological and psychiatric findings in 86 cases of congenital cardiac disease and attempts to relate the majority of the disorders to oxygen lack. Of these patients, 54 were aged between 3 and 16 and 32 between 16 and 36 years. The main cardiac defects were Fallot's tetralogy (29 cases), patent ductus arteriosus (15), septal defects (9), and Eisenmenger's complex (5), while 42 cases were of the cyanosed type and 44 were non-cyanosed.

Slight neurological abnormalities consisting in mild cranial nerve palsies, poor motor coordination, and weak sensory perception were present in 64 cases, and evidence of neurovascular disturbance was found in 28 cases, these patients having severe spasmodic headaches, with pallor and vomiting. In regard to psychological abnormalities the predominant finding (82 cases) was of some degree of asthenia, these cases falling into three groups, as follows. (1) Those (37) with purely neurasthenic features of gradual onset. These patients complained of fatigue on the slightest exertion and had poor mental concentration and disturbed sleep, nightmares with a "suffocation" theme being common. Moods were variable, being either euphoric or apathetic and depressed, extremes of euphoria or apathy being noted in those in whom oxygen lack was most marked. Some patients tended to be egocentric and showed lack of normal emotion. Children were older in appearance than their years and seldom displayed enthusiasm or affection. Hypochondria and apprehension about the course of the illness were not features of this group. (2) The second group of 36 patients showed neurasthenia with a variable degree of mental retardation, which in many had been noted from a very early age; there was one case of imbecility. In 7 cases, however, mental retardation did not become apparent until the age of 10 to 12 years. (3) The notable abnormality in the third group (9 cases) was the psychotic features. In many of these patients irritability, restlessness, and

aggressiveness had been noted in early childhood; threats of violence were, however, rarely translated into action. Grandiose ideas were a feature of patients in this group.

In all the cases studied the blood oxygen content and pulmonary gaseous exchange were determined. Reference is made to the literature dealing with the effects of experimental anoxia on cerebral activity, and it is pointed out that the reported effects were very similar to many of the neurasthenic features found in these patients with congenital cardiac disease. In those showing mental retardation this was usually associated with physical abnormality and is considered to have been due to congenital cerebral abnormalities. The character defects seen in Group 3 were no doubt enhanced by oxygen deficiency, but may have been primarily due to faulty upbringing.

Margot G. Dunlop

CORONARY DISEASE AND MYOCARDIAL INFARCTION

890. Some Factors Associated with the Development of Coronary Heart Disease—Six Years' Follow-up Experience in the Framingham Study

T. R. DAWBER, W. B. KANNEL, N. REVOTSKIE, J. STOKES III, A. KAGAN, and T. GORDON. *American Journal of Public Health [Amer. J. publ. Hlth]* 49, 1349–1356, Oct., 1959. 7 refs.

The original plan of the study instituted by the U.S. National Heart Institute at Framingham, Massachusetts, was to examine medically a 2 in 3 random sample of the population aged 29 to 62 years and to re-examine at 2-year intervals over a period of 20 years those found initially to be free from cardiovascular disease. Out of 6,510 persons selected, only 4,469 (69%) responded. Of these, 4,393 were free from coronary heart disease (C.H.D.) and this number was increased to 5,127 by the addition of 734 volunteers.

In this report—the fifth to be published—discussion is restricted to the age group 45 to 62 years, consisting of 1,037 persons, and to the first 6 years of observation. During this period 94 of this group developed new C.H.D. manifested by (1) sudden death, (2) myocardial infarction, or (3) angina pectoris. The incidence varied with educational status, being less at the higher educational levels. [This is in contrast to the social class gradient of mortality from C.H.D. in England and Wales, where the rate is lowest in the less well-to-do sections of the population.] On the other hand on studying geographical distribution the lowest rate was found in an area where there was a low educational rating. On the basis of the small number of new cases which have occurred so far no association between the incidence of C.H.D. and place of birth and nationality could be demonstrated.

The incidence of new C.H.D. causing sudden death and myocardial infarction (62 cases), but not that of angina pectoris (32 cases), showed an association with cigarette consumption. It increased from 38 per 1,000 among those who smoked less than 10 per day to 63

per 1,000 in the group who smoked 10 to 20 per day and to 71 per 1,000 among still heavier smokers. Mortality from all types, including angina, increased somewhat similarly. Other findings were that the serum cholesterol level tended to be higher and the relative weight slightly lower in cigarette smokers than in non-smokers. High alcohol consumption was associated with heavy smoking, but it could not be demonstrated that alcohol consumption *per se* was associated with the incidence of C.H.D.

[In the preceding report on this survey (see Abstract 881) the conclusion was reached that although the 30% of the initial sample who refused to collaborate were overweighted with unhealthy lives, any bias arising therefrom was of little import in this survey. Nevertheless, unless it was established (and this has not been indicated) that the non-responders were distributed proportionately by geographical area, educational status, nationality, smoking habits, and so on, the results of the present paper may be biased. If, for example, the relatively unhealthy non-responders not included here belonged to the higher educational grades this might contribute in part at least to the lower incidence of C.H.D. found in these grades among the responders studied.]

E. Lewis-Fanning

891. Multiple Serial Enzyme Studies in Acute Myocardial Infarction

N. R. ROWELL and A. J. SMITH. *British Medical Journal [Brit. med. J.]* 2, 459–463, Sept. 19, 1959. 18 refs.

At the Royal Victoria Infirmary, Newcastle upon Tyne, blood levels of four enzymes were determined after acute uncomplicated myocardial infarction in 28 cases. Blood was collected daily for at least 10 days and the serum glutamic pyruvic transaminase (S.G.P.T.), serum glutamic oxalacetic transaminase (S.G.O.T.), and in some cases serum aldolase and serum oxidase activity estimated, all four being measured in the same sample of blood whenever possible. The S.G.O.T. and S.G.P.T. levels were estimated simultaneously by the methods of Reitman and Frankel, the serum aldolase level by the method of Bruns, and the serum oxidase level by the method of Ravin. (A close correlation exists between the serum oxidase activity and serum copper level, which is known to rise after acute myocardial infarction. The serum oxidase is easier to estimate than the serum copper level and probably gives the same information.) The levels of these enzymes were also estimated in 50 healthy subjects, and a level twice the standard deviation above the mean normal value was accepted as abnormal. On this basis the upper limits of normal for the four enzymes were found to be: S.G.O.T., 28 units; S.G.P.T., 21 units; serum aldolase, 9.2 units; and serum oxidase, 372 units.

The S.G.O.T. level was found to rise within 3 hours of infarction, the peak being reached on the second day after the episode and its height being roughly proportional to the extent of the infarction. This peak was greatly increased by centrilobular necrosis of the liver, which occurred in 2 fatal cases as a result of heart failure, the level in each case being above 7,500 units. The S.G.O.T. level was increased in all cases and was con-

sidered the most useful routine index of infarction. The S.G.P.T. level was increased in 23 of the 28 cases, the maximum occurring a day later than that of S.G.O.T. and lasting a day longer. Serum aldolase activity was increased in 13 out of the 14 cases in which it was estimated; it rose rapidly like the S.G.O.T. level, then fell away, but rose to another peak 5 days later. The serum oxidase level was increased in 10 of the 13 cases in which it was estimated, rising slowly to reach a peak at the ninth day. There was no increase in the levels of any of these enzymes in cases of coronary insufficiency. It is pointed out that the two transaminases and aldolase are released into the blood in liver disease and in other types of muscle destruction besides myocardial infarction.

G. S. Crockett

892. Use of I^{131} -labelled Fat in the Study of Lipid Handling in Patients with Coronary Artery Disease
R. H. SELLER, J. BRACHFELD, H. SANDBERG, and S. BELLET. *American Journal of Medicine* [Amer. J. Med.] 27, 231-240, Aug., 1959. 2 figs., bibliography.

It is generally accepted that lipid metabolism is disturbed in atherosclerosis, but the overlap between the serum lipid values found in normal subjects and in those with atherosclerosis is considerable. In order to eliminate or to reduce this overlapping the authors, working at the Philadelphia General Hospital (University of Pennsylvania), used a glyceryl trioleate test meal labelled with radioactive iodine (I^{131}). The subjects studied were 51 normotensive male out-patients suffering from minor complaints, 20 "normal" healthy subjects, and 21 patients of comparable ages with documented myocardial infarction. Ten patients with hypercholesterolaemia, marked obesity, and intermittent claudication were also studied.

Blood samples were taken at regular intervals after the test meal in order to determine the total circulating radioactivity in the whole blood and in samples precipitated by trichloroacetic acid. The differences in the mean levels of radioactivity at peak times and at 24 hours after the test meal between the control groups and the group with myocardial infarction were statistically highly significant ($P < 0.0005$). There was an abnormal response to the test in each patient with myocardial infarction, though several of these patients had normal serum cholesterol, lipid phosphorus, and α - and β -lipoprotein levels. No significant relationship could be elicited between the test meal values and age, obesity, or hypercholesterolaemia.

Z. A. Leitner

893. Postmyocardial Infarction Syndrome
N. J. WEISER, M. KANTOR, and H. K. RUSSELL. *Circulation* [Circulation] 20, 371-380, Sept., 1959. 4 figs., 9 refs.

From the Veterans Administration Hospital, Wilkes Barre, Pennsylvania, are presented 4 cases of a syndrome first described by Dressler (*J. Amer. med. Ass.*, 1956, 160, 1379; *Abstr. Wld Med.*, 1956, 20, 366), who recently reviewed some 40 cases (*A.M.A. Arch. intern. Med.*, 1959, 103, 28; *Abstr. Wld Med.*, 1959, 26, 93). The syndrome follows myocardial infarction within days or

weeks, and the main manifestations are fever, pleuro-pericardial pain, pleural or pericardial effusion, "pneumonitis", and haemoptysis. There is an accompanying leucocytosis and a rise in the erythrocyte sedimentation rate, with cardiographic changes suggestive of pericarditis. Symptoms commonly abate within a week or two, but there may be recurrences in subsequent months.

Such findings have been variously attributed in the past to further myocardial infarction, pulmonary embolism, congestive failure, infection, or overdosage of anticoagulants. The present authors believe that closer investigation will not support such explanations. A parallel is drawn with the "post-commissurotomy syndrome" following mitral valvotomy, and one hypothesis advanced is that both syndromes are due to a hypersensitivity reaction to antigens derived from damaged myocardium. In the 4 cases here described 2 of the patients had had repeated cardiac infarcts as well as the syndrome of pleural pain or pericarditis. In one who died and came to necropsy the lung changes resembled those of atypical pneumonia, but could have been due to prolonged left ventricular failure. The authors stress that critical observation is needed to define this syndrome and to differentiate it from other possible complications of severe coronary arterial disease.

J. A. Cosh

894. Angina Pectoris. I. A Variant Form of Angina Pectoris: Preliminary Report

M. PRINZMETAL, R. KENNAMER, R. MERLISS, T. WADA, and N. BOR. *American Journal of Medicine* [Amer. J. Med.] 27, 375-388, Sept., 1959. 16 figs., 28 refs.

From the University of California School of Medicine, Los Angeles, the authors describe, on the basis of 20 personal cases and a further 12 reported in the literature, a clinical variant of Heberden's classic angina pectoris which has the following differentiating features. (1) The pain comes on when the subject is at rest or during ordinary activity and is not brought on by exercise—that is, by an increase in cardiac work. (2) Its distribution is similar to that of angina of effort, but the attack may be more severe and last longer. (3) In some cases the pain occurs at the same time each day, is cyclic in nature, and, unlike the usual angina, its waxing and waning are of equal duration. (4) As in classic angina the pain is relieved by administration of nitroglycerin or sympathetic vasodilator drugs. (5) The electrocardiogram (ECG) during a severe attack shows without exception elevation of the S-T segments in the standard leads, with reciprocal depression; this elevation disappears when the pain ceases, the ECG returning to its pre-attack pattern. (6) Ventricular arrhythmias are more common during the attacks than in classic angina. (7) If infarction subsequently occurs it does so in the same areas of the myocardium that gave rise to the elevation of the S-T segments and which were ischaemic during attacks. (8) The exercise tolerance test does not produce these changes in the ECG. (9) It is noted that angina of effort may be present in addition to the variant. (10) The pain of the variant form comes on without warning and is not brought on by emotion or other apparent cause.

The authors consider that this variant form of angina is produced by the temporary occlusion of a large diseased coronary artery, possibly the result of an increase in tone of the vessel wall. Similar ECG changes were reproduced experimentally by intermittent occlusion of a large coronary vessel in dogs. The condition is not uncommon, but is rarer than angina of effort. The occurrence of cardiac infarction abolishes the attacks of pain. It is suggested that the condition is best treated by repeated administration of nitroglycerin, together with anticoagulant and sympathetic vasodilator drugs, anti-arrhythmic agents if required, and a low-fat, low-calorie diet, with a reduction in, or preferably cessation of, smoking. In some cases attacks could be prevented by giving nylidrin hydrochloride. A monograph on the whole subject is in preparation.

[This is an important paper.]

G. S. Crockett

895. "Marsilid" in Angina Pectoris. ("Marsilid" bei Angina Pectoris) M. HOLZMANN. *Cardiologia [Cardiologia (Basel)]* 35, Suppl., 17-37, 1959. 11 figs., 46 refs.

The author reports from Zürich his results in 18 cases of angina pectoris treated with iproniazid phosphate ("marsilid") in daily oral doses of 75 to 100 mg. Two patients failed to benefit, but in 5 the results were "good" and in 11 "very good". Improvement set in within 3 to 8 days, but anginal attacks recurred within 8 to 20 days of stopping the treatment. The drug had no effect on abnormal findings in electrocardiograms (ECGs) taken during rest, but the author describes 5 cases in detail in which he noted improvement in ECGs recorded immediately after climbing stairs and then again 5 minutes later, and in which an ischaemic reaction to the coronary stenotic disease process was seen to occur earlier than did subjective anginal symptoms, and indeed sometimes in their absence. Side-effects of marsilid were frequent, and included constipation, impotence, insomnia, lassitude, vertigo, lowering of blood pressure and orthostatic hypotension, retention of body fluids, and disturbances of micturition.

In discussion the author suggests four mechanisms whereby marsilid may exert an influence on angina pectoris. (1) In some patients it gives rise to euphoria, which psychological effect he regards as of adjuvant therapeutic value. (2) It exerts a hypotensive effect, probably through blocking of sympathetic ganglia, which is of value in a minority of patients with gross restriction of movement; but in most it constitutes a real danger, especially if associated with euphoria, for since the warning signal of anginal pain is abolished patients are encouraged to exceed their capacity for effort. (3) Vagotonal stimulation, manifested in 3 of his cases by a marked bradycardia, is interpreted by the author as a sparing of the myocardium, with suppression of pain and postponement of the ischaemic reaction. (4) Since none of these mechanisms was at work in all his cases the author advances the hypothesis of a fourth mechanism, namely, that marsilid reduces the oxygen requirements of the heart, for which he claims there is experimental evidence. This hypothesis would explain

both the recurrence of angina when the drug is discontinued and those cases which deteriorate under treatment initially and then improve when it has been under way for some weeks. He stresses that marsilid is not curative, for it does not protect the arterial wall from sclerosis or prevent thrombosis; it has no dilator effect on the coronary blood vessels and cannot be used as a prophylactic against infarction. It may prove to be of special value in (1) cases of recent infarction, by reducing oxygen requirements at the periphery until the establishment of a collateral circulation and thus preventing death of the myocardium, and (2) in chronic cases of angina pectoris in which there is widespread narrowing of the coronary blood vessels, by retarding the deleterious effects.

E. S. Wyder

896. Therapeutic Experience with *iso*Propyl-isonicotinic Acid Hydrazide in Angina Pectoris. (Therapeutische Erfahrungen mit *Isopropyl-isonicotinsäurehydrazid* bei Angina pectoris) F. SCHAUB. *Cardiologia [Cardiologia (Basel)]* 35, Suppl., 56-61, 1959.

The results in 53 cases of severe angina pectoris (46 in men and 7 in women) and 32 cases of recent myocardial infarction treated with *isopropyl-isonicotinic acid hydrazide* (iproniazid; "marsilid") are reported from the Medical Clinic of the University of Zürich. Of the 44 cases in which the therapeutic effect could be assessed accurately, there was deterioration in one and little or no benefit in 14, but the symptoms were markedly relieved or disappeared in 29; 12 of the 29 had had a previous infarct and 6 had been refractory to all other forms of treatment. Marsilid was given by mouth in doses of 50 mg. thrice daily. In 8 cases the daily dose was reduced to 100 or 75 mg. without recurrence of symptoms. In the cases of infarction, of 11 patients to whom marsilid was given within 1 to 10 days of the occurrence of a fresh myocardial infarct, 7 were promptly relieved of all symptoms. Of 21 patients with pathological changes in the electrocardiogram, none showed any change while under treatment.

Only 7 out of 41 patients showed no side-effects. In the remainder there occurred, in order of frequency, gastro-intestinal symptoms (constipation, flatulence, or dryness of the mouth), hypotension, disturbances of micturition (dysuria or polyuria), impotence, euphoria, lassitude, and muscle cramps. Orthostatic disturbances were not met with, as these patients were confined to bed. In 6 of the 8 cases in which the dosage was lowered the side-effects were correspondingly reduced. However, 2 patients who had reacted well to marsilid died of myocardial infarction a few days after treatment was stopped, and a third patient died in status anginosus owing to a fall in the blood pressure while still under treatment. The author does not believe that these 3 fatal cases could be attributed to the effects of the drug. Although he is impressed with the results of marsilid in angina pectoris, equalled hitherto only by those of nitroglycerin in acute attacks, the author recommends that the drug should be given only in severe cases on account of its disturbing side-effects.

E. S. Wyder

PERIPHERAL ARTERIES

897. Placental Implantation for Peripheral Vascular Disease

C. W. A. FALCONER and A. A. GUNN. *British Medical Journal* [Brit. med. J.] 2, 538-541, Sept. 26, 1959. 3 figs., 8 refs.

This paper from the Western General Hospital, Edinburgh, reports a preliminary trial of the implantation of placental tissue for the treatment of peripheral vascular disease. Into the thigh of the more seriously affected limb of 39 patients with intermittent claudication three 1-cm. cubes of tissue from the cotyledon surface of a fresh placenta were implanted after incubation at 4° C. with penicillin and saline for 5 days; at the same time four control groups received the saline and penicillin solution only, a saline extract of placenta, a saline extract of foreign-body protein, and ethinyloestradiol respectively.

There was a rapid subjective improvement in 27 of the 39 patients treated with placental implant, this improvement being confirmed objectively by increased exercise tolerance, as measured by claudication distance, and by the results of reflex heating tests. However, oscillometric improvement was noted only in 2 out of 28 cases, and in no case did the peripheral pulse improve, but in 4 cases long-standing resistant lesions (necrosis in 2 cases and ulcer in 2) healed and remained healed. In the control groups 3 out of 5 patients receiving placental saline extract and 3 out of 8 given ethinyloestradiol were improved. No improvement was noted in the other two control groups, but when these patients were subsequently given placental tissue implants 8 out of 9 improved. In the patients who improved after initial treatment with placental tissue the average duration of improvement was about 10 (range 3 to 24) months. Of 5 who relapsed after the first treatment, 3 later responded satisfactorily to a second implantation. The duration of response of those patients receiving saline extract of placenta or oestradiol was only temporary.

The precise mechanism of the action of placental tissue is not clear, but is probably not due to improved collateral circulation. The authors suggest that the active principle may be ethinyloestradiol, but this requires confirmation. Urinary gonadotrophin excretion assayed in one patient who responded to placental implantation was found to be unchanged.

[The therapeutic results of this trial seem in general to be very satisfactory, but the number of cases is perhaps rather small.]

Leon Gillis

898. Glutamic Oxalacetic Transaminase in Chronic and Acute Peripheral Artery Occlusion: Clinical and Experimental Study

G. A. FERUGLIO, S. BELLET, and L. J. FEINBERG. *American Journal of Cardiology* [Amer. J. Cardiol.] 4, 211-217, Aug., 1959. 2 figs., 19 refs.

Serum glutamic oxalacetic transaminase [SGO-T] activity was studied in 35 cases of chronic peripheral arterial disease [at Philadelphia General Hospital]. Group I consisted of 16 patients with a moderate degree

of peripheral arterial insufficiency. Group II consisted of 19 patients who had associated gangrene of the lower extremities. No significant increase in SGO-T level was noted in the first group of patients. A significant increase in the SGO-T level observed in only 3 subjects in the second group could be explained by the presence of associated acute myocardial infarction (one case) and liver damage (2 cases). Blood samples drawn simultaneously from the femoral artery and the femoral vein showed no significant differences in SGO-T levels.

These findings suggest that in patients with peripheral vascular disease, with or without subacute or chronic gangrene, the occasional appearance of elevated SGO-T levels is probably the result of factors other than the peripheral vascular involvement, usually acute damage to the heart or liver. Acute occlusion of a major artery in 7 of 9 patients and in the hind limbs of experimental animals was followed by a significant elevation of SGO-T levels.—[Authors' summary.]

899. Use of a New Vasodilator Agent in Management of Peripheral Arterial Insufficiency

S. S. SAMUELS and H. E. SHAFTEL. *Journal of the American Medical Association* [J. Amer. med. Ass.] 171, 142-145, Sept. 12, 1959. 11 refs.

The authors describe the vasodilator properties of a new hydroxyephedrine derivative, isoxsuprine hydrochloride ("vasodilan"), and report the results obtained with this drug in the treatment of 46 patients with arteriosclerosis. The patients were aged 41 to 77 years and 30 were females. Gangrene was present in 3 cases. Objective improvement was assessed from walking capacity, healing of gangrene, and the results of digital plethysmography and of oscillometric estimation of the blood flow in the leg. The drug was given by mouth in a dosage of 10 to 20 mg. 3 times daily for periods ranging from 3 weeks to 18 months. No untoward side-effects or contraindications were observed. In general the results confirmed those of previous workers who noted increased claudication distance and blood flow (estimated plethysmographically and oscillometrically as well as by other methods) when patients with peripheral vascular insufficiency were treated with isoxsuprine. In the authors' view the drug seems to be well suited to outpatient management of these cases.

[In view of the present scepticism concerning the value of vasodilators this substance would appear to be worth a further trial.]

Leon Gillis

900. An Evaluation of the Various Peripheral Dilators Used in the Treatment of Intermittent Claudication

R. O. GILLHESPY. *British Journal of Clinical Practice* [Brit. J. clin. Pract.] 13, 608-611, Sept., 1959. 10 refs.

An account is given of the chemical composition, mode of action, and results of clinical trials of the various vasodilator drugs used by the author at the Peripheral Vascular Disease Clinic, Birmingham, in the treatment of intermittent claudication secondary to arteriosclerosis, these being "cyclospasmol" (spasmocycline), "ilidar" (azapetine phosphate), "ronicol" (nicotiny alcohol), "perdilatal" (buphenine hydrochloride), and "priscol"

(tolazoline hydrochloride). Vitamin E (α -tocopherol) was also tried, but was found to be useless.

(1) Spasmocycline acts like papaverine, but is twice as effective; it is of extremely low toxicity. (2) Azapetine phosphate blocks the vasoconstrictor responses to adrenaline, to noradrenaline, and to sympathetic nerve impulses in skeletal muscle. (3) The vasodilator properties of ronicol are essentially the same as those of nicotinic acid, but its action is more sustained; its vasodilator effect is mainly on the smaller arteries and arterioles. (4) Perdilatal acts on the vessels of the musculature like adrenaline, increasing the muscle blood flow according to some authorities, but Riddell and others concluded that it acts mainly on the vessels of the skin rather than those of the muscles. (5) Priscol causes an immediate reduction in muscle blood flow which coincides with an increase in skin blood flow.

The author's tabulated results show that cyclospasmol is the most effective single drug, improvement being obtained in 78% of cases treated with it. This drug acts relatively slowly, however, but if combined with ronicol, which acts more quickly, the action of each is enhanced. Ilidar is said to show "considerable promise", while perdilatal and priscol were useful in selected cases.

Leon Gillis

HYPERTENSION

901. **Untreated and Treated Patients with Hypertension** J. H. MOYER and A. BRÉST. *Diseases of the Chest [Dis. Chest]* 36, 297-314, Sept., 1959. 10 figs., 3 refs.

Writing from Hahnemann Medical College, Philadelphia, the authors review the course, treatment, results, and long-term effects of elevated blood pressure, notably on renal haemodynamics. Hypertension leads to vascular damage particularly in the brain, heart, and kidneys, the last-named being possibly the most sensitive in this respect. In 129 untreated hypertensive patients the blood pressure (measured by intra-arterial manometry) was shown to be inversely related to the glomerular filtration rate (measured by inulin clearance), there being a direct relationship between severity of the hypertension and degree of renal vascular deterioration. Treatment of malignant and severe non-malignant hypertension with hypotensive drugs is particularly valuable in arresting renal vascular damage and preventing death in uraemia. In the authors' series of treated cases of non-malignant hypertension the commonest cause of death was cerebral vascular accident, while deaths from uraemia were rare, whereas in the untreated cases uraemia was commoner than cerebral vascular accident.

The authors usually treat hypertensive crises with parenteral reserpine or ganglion-blocking agents, subsequent control of the blood pressure being obtained by treatment with chlorothiazide and reserpine, with the addition when necessary of a ganglion-blocking agent. Constipation can be prevented by giving milk of magnesia or cascara sagrada, separately or together. If ileus develops as the result of ganglionic blockade 1 mg. of neostigmine may be given parenterally every hour until bowel movement occurs. The reduction of blood pres-

sure should be related inversely to the blood urea level. Long-acting ganglion-blocking agents should be given in smaller dosage at night time to prevent postural morning hypotension. The dosage of hypotensive drugs may have to vary in proportion with the patient's changing environmental stress, which can often be lessened by the therapist offering "every day psychiatric assistance to his patient".

K. G. Lowe

902. **Evaluation of 2 Monoamine Oxidase Inhibitors (Iproniazid and JB 516) in the Therapy of Arterial Hypertension**

H. H. ORVIS, I. G. TAMAGNA, and R. E. THOMAS. *American Journal of the Medical Sciences [Amer. J. med. Sci.]* 238, 336-343, Sept., 1959. 1 fig., 16 refs.

Iproniazid and a related compound, 1-phenyl-2-hydrazinopropane (JB 516), were given singly or each in combination with chlorothiazide to 8 patients with established diastolic hypertension at George Washington University Hospital, Washington, D.C. There was a significant fall in sitting and in standing diastolic pressure with iproniazid in a dosage of 150 mg. daily and also with half this dosage of iproniazid combined with 1 g. daily of chlorothiazide. Similar results were achieved with JB 516 in a dosage of 12.5 mg. daily. The compounds were slow in action, and orthostatic hypotension did not become manifest until the third week of treatment with iproniazid, although this was shortened to one to 2 weeks when chlorothiazide was given in addition. JB 516 with or without chlorothiazide was effective in one to 2 weeks. Constipation and insomnia were the most frequent side-effects, the latter responding to small doses of phenobarbitone at bedtime. There was no significant change in the serum total cholesterol level during the 10 weeks of treatment with JB 516.

It is suggested that these compounds with monoamine oxidase inhibiting properties may prove useful in the investigation and treatment of hypertension.

G. S. Crockett

903. **Study of the Action of Reserpyl Trimethoxycinnamate in 73 Cases of Hypertension.** (Étude de l'action du triméthoxy-cinnamate de réserpyl chez 73 sujets hypertendus)

J. VIGNALOU, P. BERTHAUX, and P. LAFFLY. *Presse médicale [Presse méd.]* 67, 1698-1699, Oct. 3, 1959. 1 fig., 15 refs.

This study was carried out at the Hospice d'Ivry, a home for old age pensioners and the chronic sick in Paris, on 73 female inmates between the ages of 52 and 85 (mean 73) years. All patients in the home with a minimum diastolic pressure of 110 mm. Hg were included in the series; the mean of six separate readings obtained during the month preceding the start of the treatment was taken as the basis for comparison. All patients initially received a dose twice daily of 1 mg. of reserpyl trimethoxycinnamate, another alkaloid of *Rauwolfia* similar in action to reserpine. In 20 cases in which no reduction of blood pressure was observed after 4 to 6 weeks the daily dose was increased to 3 mg., resulting in 15 cases in an appreciable fall in pressure. In 26 cases in which the

diastolic pressure fell to 80 mm. Hg or lower the dose was reduced to 1 mg. daily or the drug withdrawn.

The period of observation was 3 months. In 55 patients a fall in diastolic pressure of at least 20 mm. Hg was obtained. Of 47 patients who had complained of headaches, vertigo, or tinnitus, 27 now reported symptomatic improvement. Bradycardia was noted in 21 cases, but the only undesirable side-effect was nausea in one patient. The loss of appetite and nasal congestion reported by other authors was not observed in this series.

H. F. Reichenfeld

904. Significance of Findings in the Fundus in Vascular Hypertension. (Význam nálezu na očním pozadí u hypertenzní nemoci)

J. SVĚŘÁK and M. VAVŘÍK. *Časopis lékařů českých [Čas. Lék. Čes.]* 44, 1381-1385, Oct., 1959. 3 figs., 24 refs.

The authors examined 203 patients with hypertension and compared the incidence of pathological changes in the fundus with the duration of the disease, the degree of diastolic hypertension, and the pathological findings in the heart and kidneys. A direct relationship was found between both the duration of the hypertension and the height of the diastolic pressure on the one side and the degree of change in the optic fundus on the other, the diastolic hypertension being more significant than the duration of the disease. This relationship becomes clear in the statistical evaluation of large groups, but not in the evaluation of the individual case. Thus of one group of patients who had had the disease for more than 3 years and had a diastolic pressure of over 110 mm. Hg, in at least 8% the fundus findings were physiological (14% change, the 1st degree according to Keith and Wagener's classification). Pathological changes in the heart due to hypertension clearly precede those in the fundus. The relationship between changes in the fundus and changes in the kidneys is also clear when large groups are evaluated statistically. In an individual case only fundal changes of the 3rd and 4th degree are of importance as indicating a high diastolic pressure or long duration of the disease, or both.

M. Klima

905. Hysterical Laryngeal Spasm and the Production of Paroxysmal Arterial Hypertension

J. H. TYRER, B. T. EMMERSON, and K. J. MURPHY. *Quarterly Journal of Medicine [Quart. J. Med.]* 28, 315-328, July [received Sept.], 1959. 5 figs., 43 refs.

Hysterical laryngeal spasm is described in 2 patients. In the first patient the spasm was purely expiratory. In the second patient attacks began with inspiratory laryngeal spasm, but expiratory laryngeal spasm usually became added and dominant if the hysterical attack lasted longer than about 10 minutes.

Attention is drawn to an unusual type of paroxysmal arterial hypertension encountered in these patients. Forced obstructed expirations, in relation to hysterical expiratory adductor spasm of the vocal cords, caused severe arterial hypertension during the prolonged expirations; this arterial hypertension remitted during every short inspiration. The first patient had been referred for consideration of a possible phaeochromocytoma.

The second patient had been regarded as having essential hypertension during a number of previous observations in hospital, but between attacks of laryngeal spasm he was clearly normotensive. After practice, three apparently normal men could closely simulate the hysterical attacks as regards the pattern and severity of the arterial hypertension as well as other features.—[Authors' summary.]

PULMONARY CIRCULATION

906. The Treatment of Pulmonary Embolism with Fibrinolysin

A. L. SHEFFER and H. L. ISRAEL. *Angiology [Angiology]* 10, 292-298, Aug., 1959. 10 figs., 12 refs.

An investigation was carried out at the Graduate Hospital, University of Pennsylvania, Philadelphia, to determine the efficacy of intravenous administration of fibrinolysin, with or without anticoagulants, in the treatment of pulmonary embolism. Only 6 cases of pulmonary embolism were treated, but in order to observe the side-effects of fibrinolysin 26 other patients with acute or chronic thrombophlebitis, retinal vein thrombosis, arterial occlusion, or cerebral thrombosis were also treated. The efficacy of the enzyme was assessed on the basis of: (1) the rapidity of radiological resolution of the pulmonary shadows which were found in 80% of a control series; (2) the rapidity with which cardio-respiratory or peripheral vascular symptoms resolved; (3) the rapidity with which changes in the electrocardiogram disappeared; and (4) the incidence of embolic phenomena following treatment.

The fibrinolysin was given in doses of 25,000 to 50,000 units, increased later to 50,000 to 100,000 units, in 500 ml. of 5% dextrose-saline over 2 to 4 hours on successive days. Routine laboratory estimations included haemoglobin concentration, complete blood count, blood prothrombin and coagulation times, and the blood urea nitrogen and fasting blood sugar levels; urine analysis, radiological examination of the chest, and electrocardiography were also carried out.

Febrile reactions following the infusions occurred in 27 of the cases, and in 2 patients not receiving anticoagulants pulmonary infarction occurred subsequently. There were no other changes in the results of the various routine investigations after treatment. The authors reach no definite conclusions, but the results suggest that fibrinolysin by itself may not prevent recurrent embolism. Compared with the results in a control series of cases the drug appears to increase the rate of resolution of the pulmonary infarction. In thrombo-embolic disease elsewhere in the body fibrinolysin may give fairly constant relief of the acute symptoms, but only transient relief of those related to long-standing disease. It is suggested that the enzyme may prove useful as a supplement to anticoagulant therapy.

[As the authors themselves stress, this series of cases is too small for an accurate estimation of the effect of fibrinolysin in cases of pulmonary embolism to be made.]

R. Wyburn-Mason

Clinical Haematology

907. Clinical and Haematological Aspects of Macroglobulinaemia Waldenström. [In English]

J. W. IMHOF, H. BAARS, and M. C. VERLOOP. *Acta medica Scandinavica* [Acta med. scand.] 163, 349-366, 1959. 1 fig., 30 refs.

The authors discuss the clinical and haematological picture of Waldenström's macroglobulinaemia with reference to 107 cases described in the literature, and report in detail 7 new cases seen at the University Hospital, Utrecht, since 1953.

There appears to be a significant ($P < 0.01$) male preponderance (68:39), while more than 75% of the 107 patients were over 50 years old. A rapidly fatal clinical course is exceptional, the disease usually taking a chronic course. The clinical picture is dominated by anaemia, a haemorrhagic diathesis, lymphadenopathy, and hepatosplenomegaly. Bone pains and spontaneous fractures are uncommon; osteoporosis may occur, but this is not uncommon in patients over 50 years old; mild osteolytic lesions have been described, but not the typical, sharply circumscribed, larger lesions seen in multiple myeloma. Cryoglobulinaemia may occur (in 16 cases) and in these cases a complete Raynaud's syndrome may develop. Neurological disturbances (14 cases) and Bence Jones proteinuria (13 cases) may occur, while the coexistence of malignant tumours was noted in 9 cases.

The cause of the anaemia varies; disturbed erythropoiesis and loss of blood by the haemorrhagic diathesis are important factors. In 6 cases described in the literature and in 2 of the authors' cases there was a marked haemolytic element. The leucocyte count is usually normal, though there may be a lymphocytosis and in the bone marrow there is often an increase in lymphatic cells, but in 9 cases from the literature and one of the authors' cases pancytopenia was present. In 33 cases thrombocytopenia was present, which might account for the haemorrhagic diathesis, but in many cases haemorrhages occur in the presence of a normal platelet count. The various theories which have been put forward to account for this bleeding tendency are discussed by the authors.

Victor M. Rosenoer

908. Involvement of the Nervous System in Polycythaemia, Pernicious Anaemia, and Leukaemia. (О поражении нервной системы при полицитемии, анемии Бирмера и лейкозах)

T. K. KADYROVA. *Клиническая Медицина* [Klin. Med. (Mosk.)] 37, 132-137, Sept., 1959.

The association of neurological syndromes with pernicious anaemia is well recognized, but the changes in the nervous system in polycythaemia and leukaemia have attracted less attention.

In polycythaemia the increased mass of blood and its great viscosity leads to disturbance of the cerebral circulation with subjective symptoms such as lethargy, as-

themia, headache, tinnitus, and impairment of memory, as well as vague pains in various parts of the body. This may lead to an erroneous diagnosis of neurasthenia. In more advanced cases pareses or even hemiplegia may occur, usually associated with cerebral haemorrhage; or there may be psychological changes such as confusion, hallucination, and alternating excitement and stupor.

In addition to subacute combined degeneration of the spinal cord pernicious anaemia may be associated with nervous changes such as polyneuritis. Psychological changes are not uncommon, but involvement of the cranial nerves is rare. In the early stages these neurological complications respond well to adequate dosage of vitamin B₁₂ (cyanocobalamin).

The nervous complications of leukaemia are characterized by their extreme polymorphism. In acute leukaemia both subarachnoid and cerebral haemorrhages are common, while in that type of the disease which manifests itself in ulcerative and necrotizing lesions myelitis and meningo-encephalitis occur. In the chronic form the nervous symptoms may simulate those of neurasthenia, as in polycythaemia, or there may be isolated nervous disturbances such as nerve deafness, Ménière's syndrome, trigeminal neuralgia, sciatica, and intercostal neuralgia. In the later stages vegetative disturbances such as hyperidrosis, dermatographism, polydipsia, and Horner's syndrome are common. The diversity of these symptoms is accounted for by the infiltration of tissues, including those of the nervous system. L. Firman-Edwards

909. Hereditary Hemorrhagic Telangiectasia and Pulmonary Arteriovenous Fistula: Survey of a Large Family C. H. HODGSON, H. B. BURCHELL, C. A. GOOD, and O. T. CLAGETT. *New England Journal of Medicine* [New Engl. J. Med.] 261, 625-636, Sept. 24, 1959. 7 figs., bibliography.

In this paper from the Mayo Clinic a review of the available data on hereditary telangiectasia is followed by a study of a large family of which many members had this disease. Information concerning the presence or absence of telangiectasia was obtained in respect of 231 out of 331 known members of the family, and 91 (34.4%) of these had telangiectasia. The incidence in males and females was approximately equal, and the disease was transmitted by both sexes alike. Telangiectasia was rarely recognized early in life, but became progressively more apparent with age. All generations were involved except the sixth, absence of the disease in this generation being explained by the fact that all the members were children under 10 years of age. Pulmonary arteriovenous fistula occurred in 14 patients (6.1% of the family group and 15.4% of those with telangiectasia). The seriousness of the pulmonary manifestations is emphasized; of the 14 patients, one died

from cerebral abscess, one died from massive haemothorax, and 2 had non-fatal haemoptysis. A significant number of patients with telangiectasia but without pulmonary arteriovenous fistula suffered from such complications as frequent epistaxis, alimentary haemorrhage, and cerebral lesions. It is suggested that in all members of a family in which hereditary telangiectasia occurs the thorax should be examined radiologically at intervals to determine the presence or absence of pulmonary arteriovenous fistula. Surgical removal of the fistula should be undertaken in cases with enlarging lesions, haemoptysis, haemothorax, blood-stream infections, or abscess.

The gravity of homozygous inheritance of telangiectasia is stressed, and it is urged that members of an affected family should not marry members of a similarly affected family because a lethal form of the disease is likely to be passed on to the children. *J. L. Markson*

910. Inherited Hemorrhagic Disorder with Antihemophilic Globulin Deficiency and Prolonged Bleeding Time (Vascular Hemophilia)

C. L. SPURLING and M. S. SACKS. *New England Journal of Medicine* [New Engl. J. Med.] 261, 311-319, Aug. 13, 1959. 8 figs., 39 refs.

In this paper from the University of Maryland School of Medicine, Baltimore, the authors describe 2 cases of the dual haemostatic defect termed "vascular haemophilia" and discuss the nature of the defects and certain controversial issues such as hereditary transmission and the relationship between this disorder and pseudo-haemophilia and Willebrand's disease. In both patients there was a deficiency of antihemophilic globulin associated with a prolonged bleeding time. The Bridge anticoagulant effect was observed in one of the cases.

A. Brown

ANAEMIA

911. Oral Treatment of Pernicious Anaemia with Vitamin B₁₂ and Desiccated Hog Duodenal Extract

E. K. BLACKBURN, G. H. SPRAY, H. T. SWAN, G. R. TUDHOPE, and G. M. WILSON. *British Medical Journal* [Brit. med. J.] 2, 535-538, Sept. 26, 1959. 18 refs.

The results of prolonged oral administration of vitamin B₁₂ (cyanocobalamin) and desiccated extract of hog duodenal mucosa to 22 patients with pernicious anaemia are reported. The drugs were given in tablets of "biopar" or "biopar forte", each tablet of the former containing 6 µg. of vitamin B₁₂ and 30 mg. of the intrinsic factor preparation and each tablet of biopar forte containing 15 µg. of vitamin B₁₂ and 35 mg. of the intrinsic factor preparation. A group of 13 patients who had been satisfactorily maintained by parenteral administration of vitamin B₁₂ were transferred to biopar therapy, receiving one tablet daily for 1½ years, then 2 tablets daily for one year, and finally 2 tablets of biopar forte daily for 2½ years. Of 9 patients with untreated pernicious anaemia, 4 were given 5 tablets daily for 2 to 9 months, when they were transferred to the same dosage schedule as the group of 13 treated patients. The remaining 5 untreated patients received 5 tablets of

biopar forte daily for 6 months and then continued treatment with 2 tablets daily.

Haematological relapse occurred in 3 out of 17 patients after treatment for 2½ to 5 years. In the remainder, except for 2 patients who developed a concomitant iron-deficiency anaemia which responded to iron, the erythrocyte count and haemoglobin level remained within the normal range during treatment. The marrow showed well-marked megaloblastic change in 6 out of 17 cases within 5 years, while minor but not diagnostic abnormalities were detected in a further 6. The serum vitamin B₁₂ level was below the normal lower limit of 150 µg. per ml. in 16 of the 22 patients. In the 9 cases of previously untreated pernicious anaemia there was a satisfactory initial response, but after 6 to 17 months' treatment the serum vitamin B₁₂ level was abnormally low in 3 out of 5 cases. No neurological complications occurred. The results of skin tests with an extract of hog duodenal mucosa showed no relationship between skin sensitivity and refractoriness to treatment.

It is concluded that neither biopar nor biopar forte is reliable in the maintenance treatment of pernicious anaemia. *J. L. Markson*

912. Intestinal Absorption of Liver-bound Radiovitamin B₁₂ in Patients with Pernicious Anaemia and in Controls
P. G. REIZENSTEIN and W. NYBERG. *Lancet* [Lancet] 2, 248-252, Sept. 5, 1959. 2 figs., 35 refs.

This paper from Karolinska Sjukhuset, Stockholm, and the Central Hospital, Vasa, Finland, describes investigations in which a non-dialysable form of vitamin B₁₂ (cyanocobalamin) labelled with ⁶⁰Co prepared from the livers of pigs or calves given labelled vitamin B₁₂ was administered orally to 11 normal control patients and 10 patients suffering from pernicious anaemia. Faeces were collected for the next 7 to 11 days and their ⁶⁰Co content determined. The same subjects were later given crystalline labelled vitamin B₁₂ by mouth and the faecal excretion again determined. In the controls the average intake of liver-bound vitamin B₁₂ was 22 µg. and retention was 6 µg. (mean retention 30%). With crystalline vitamin B₁₂ the mean intake was 37 µg. and retention 3 µg. (17%). A similar difference was observed in the patients with pernicious anaemia, a mean intake of 20 µg. of liver-bound vitamin B₁₂ resulting in a mean retention of 9 µg. (36%) and a mean intake of 20 µg. of crystalline vitamin B₁₂ resulting in a mean retention of 2 µg. (7%).

These results, if confirmed, show that liver-bound vitamin B₁₂ is absorbed better than crystalline vitamin B₁₂ both by normal subjects and by patients with pernicious anaemia. Such preparations may be of value in the treatment of this disease.

[The tables showing the results of the retention estimations as given in the paper are difficult to follow, and the reported percentages of vitamin B₁₂ retained do not agree with those calculated from the data presented. Further, the small number of subjects studied makes it unwise to draw conclusions from statistical tests of significance.]

M. Lubran

913. Acetazolamide in the Treatment of Sickle-cell Anaemia

L. G. MACDOUGALL and G. JACOB. *British Medical Journal* [Brit. med. J.] 2, 141, Aug. 8, 1959. 1 ref.

The authors report 3 cases of sickle-cell anaemia in children treated with acetazolamide at King George VI Hospital, Nairobi. The drug was given in doses of 10 mg. every 6 hours and treatment continued for as long as 35 days. In none of the cases was a rise in haemoglobin level observed, and one patient actually went into crisis. The authors conclude that the therapeutic value of acetazolamide in this disease "is open to doubt".

Janet Vaughan

POLYCYTHAEMIA

914. Polycythaemia Vera and Its Treatment with Radioactive Phosphorus

L. SZUR, S. M. LEWIS, and A. W. G. GOOLDEN. *Quarterly Journal of Medicine* [Quart. J. Med.] 28, 397-424, July [received Sept.], 1959. 13 figs., bibliography.

The clinical and haematological findings and the results of treatment with radioactive phosphorus in 90 patients suffering from polycythaemia vera seen at Hammersmith Hospital (Postgraduate Medical School of London) since 1949 are reviewed. The majority of the patients were between 50 and 70 years of age, the sexes were almost equally represented, and only 3 patients gave a family history of polycythaemia vera or leukaemia. Commonly 2 to 5 years had elapsed between the onset of symptoms and diagnosis.

Plethora was an almost universal sign, with suffusion of the conjunctivae and cyanosis. The diastolic blood pressure exceeded 100 mm. Hg. in 31 cases, this hypertension being reversible in the early stages. There was no evidence to support the subdivision of polycythaemia vera into normotensive and hypertensive types. Splenomegaly was detected in 69 patients (77%), hepatomegaly in 47 (52%), and glossitis and buccal ulceration in some. Dyspepsia was common, but only 8 patients were shown to have peptic ulcer. Five had typical gout. Haemorrhage or thrombosis in various sites was a frequent and often a dangerous complication.

The essential criterion for the diagnosis is an increase in the erythrocyte mass; this was determined by calculation from the blood volume as estimated with erythrocytes labelled with ^{51}Cr , the values ranging from 30 to 92 ml. per kg. body weight (normal 28 to 35 ml. per kg.). Erythrocyte survival, estimated by the same technique, was found to be normal. The mean corpuscular haemoglobin concentration was subnormal in 78% of cases. There was a leucocytosis in 71% and thrombocytosis in only 50%. Although haemorrhage and thrombosis were particularly common in the 8 patients whose platelet count exceeded 1 million per c.mm., there were no grounds for considering these patients to have a separate disease which some haematologists would call essential thrombocythaemia. The bone marrow was normal in 18% of cases and in 33% showed typical crowding and normoblastic hyperplasia. The marrow iron was depleted in 80%. Bone biopsy. was found useful—for

example, in showing the increased reticulin of myelofibrosis.

The treatment of choice is with ^{32}P , though venesection may be required to reduce the blood volume rapidly or if ^{32}P treatment fails. Chemotherapy is unsatisfactory. After the intravenous (or oral) administration of 4 to 7 mc. of ^{32}P the erythrocyte count takes at least 6 to 8 weeks to fall, and 4 months should elapse before another dose is given. Full remission for not less than 6 months was obtained in 64 cases (82%) after 1 to 3 injections, partial remission in 13%, and no remission in only 4%. The average remission lasted 22 months (at least) and further therapy with ^{32}P produced results as good as those of the initial treatment.

Altogether 19 patients have died, 7 of haemorrhage or thrombosis, 2 of leukaemia (both having had previous external irradiation), and one with myelofibrosis. It is difficult to estimate the prolongation of life with modern treatment.

T. B. Begg

NEOPLASTIC DISEASES

915. Haemolytic Syndromes in Malignant Blood Diseases. A Study of Erythrocyte Agglutination Tests in the Course of These Conditions. (Les syndromes hémolytiques au cours des hémopathies malignes. Étude des tests d'agglutination érythrocytaire au cours de ces états)

J. BOUSSER and G. PEAN. *Semaine des hôpitaux de Paris* [Sem. Hôp. Paris] 35, 2578-2580, Sept. 18, 1959. 6 refs.

The triple aim of this investigation reported from the Hôtel-Dieu, Paris, was (1) to determine the frequency of symptomatic haemolytic disorders in various blood diseases, (2) to assess the value of tests for abnormal erythrocyte agglutinins in such cases, and (3) to observe the frequency with which these reactions are positive. A total of 144 patients with anaemia of various degrees were studied after the exclusion of those with congenital haemolytic anaemias, idiopathic acquired haemolytic anaemia, or with haemolysis following incompatible blood transfusion. The occurrence of haemolysis was detected by observations on the serum bilirubin, urinary urobilinogen, and reticulocyte levels, alterations in erythrocyte osmotic fragility, the lack of effect of blood transfusion in some cases, the sudden appearance of anaemia, or the aggravation of an existing anaemia.

By these criteria haemolysis was present in 21 cases (14.5%), and tests for abnormal agglutinins were positive in 9 of these, there being no positive results in patients without evident haemolysis. All the 21 cases of active haemolysis occurred in patients with malignant disease, mainly in association with lymphatic leukaemia, myeloid metaplasia of the spleen, or carcinomatous deposits in bone marrow. For the most part the tests for abnormal erythrocyte agglutinins gave a positive result in patients with lymphatic leukaemia and Hodgkin's disease and a negative result in those with myeloid metaplasia and carcinomatosis. The significance of this difference is discussed. The authors accept the existence of a causal relationship between the presence of these erythrocyte

agglutinins and the occurrence of haemolysis and proceed to postulate an entirely separate mechanism of erythrocyte destruction in those cases in which there are no demonstrable antibodies.

A. G. Baikie

916. The Clinical Implications of Hypogammaglobulinemia in Patients with Chronic Lymphocytic Leukemia and Lymphocytic Lymphosarcoma

J. E. ULTMANN, W. FISH, E. OSSERMAN, and A. GELLHORN. *Annals of Internal Medicine* [Ann. intern. Med.] 51, 501-516, Sept., 1959. 12 refs.

Significant hypogammaglobulinaemia is sometimes observed in cases of chronic lymphocytic leukaemia. There is, however, some doubt concerning the true incidence since in reported investigations of cases of chronic lymphocytic leukaemia the incidence of hypogammaglobulinaemia varies between 16 and 70%. It has been suggested that infectious complications occur more frequently in patients with hypogammaglobulinaemia.

The incidence and clinical implications of a low serum gamma-globulin level in chronic lymphocytic leukaemia or lymphocytic lymphosarcoma were studied in 60 patients (35 male and 25 female, aged 23 to 82 years) seen at the Francis Delafield Hospital, New York, between 1952 and 1957. Hypogammaglobulinaemia, defined as the condition in which the serum gamma-globulin level is 50% of normal or less, was present in 19 patients. The authors state that it was difficult to be certain that the degree of lymphoid involvement was directly related to the appearance of hypogammaglobulinaemia, although a low serum gamma-globulin level was usually observed later in the course of the illness. Infections occurred more frequently and lasted longer in patients with a low serum gamma-globulin level than in those in whom this level was normal. About half of the infections occurred during administration of steroids, most of them being due to *Staphylococcus aureus*. In none of the patients did a significant increase in the gamma-globulin level accompany haematological and general improvement following treatment.

A. W. H. Foxell

917. Comparison of Chlorambucil and Myleran in Chronic Lymphocytic and Granulocytic Leukemia

R. W. RUNDLES, J. GRIZZLE, W. N. BELL, C. C. CORLEY, W. B. FROMMEYER JR., B. G. GREENBERG, C. M. HUGULEY JR., G. W. JAMES III, R. JONES JR., W. E. LARSEN, V. LOEB, L. A. LEONE, J. G. PALMER, W. H. RISER JR., and S. J. WILSON. *American Journal of Medicine* [Amer. J. Med.] 27, 424-432, Sept., 1959. 2 figs., 20 refs.

The authors report a comparative trial of busulphan ("myleran") and chlorambucil in patients suffering from chronic granulocytic leukaemia—that is, with a leucocyte count of 35,000 per c.mm. and typical bone marrow—and patients with lymphocytic leukaemia—that is, a lymphocytosis of 15,000 per c.mm. on two or more occasions. The patients in both groups were either untreated or in relapse after an interval of at least 3 months since previous treatment. The presence of thrombocytopenia, a low haemoglobin level, or a positive reaction to the Coombs test contraindicated inclusion

in the trial. The drugs were dispensed in sealed envelopes, and the choice of myleran or chlorambucil was at random. The former was administered in a dosage of 6 mg. daily and chlorambucil in a dosage of 12 mg. daily, with adjustment as required, each for a period of 3 months.

Of 40 patients with chronic lymphocytic leukaemia, 17 were given an adequate trial with myleran and 23 with chlorambucil. The latter drug appeared superior, the response being excellent or good in 15 and fair in 2, whereas of the patients given myleran, 3 showed a fair response only. Moreover myleran also caused more serious bone-marrow depression than did chlorambucil. Of 42 patients with chronic granulocytic leukaemia, 21 received myleran and 21 chlorambucil. There was an excellent or good response in all 21 patients given myleran; of those given chlorambucil, the response was excellent or good in 12, fair in 8, and questionable in one.

The mode of action of the drugs and further possibilities of chemotherapy in malignant disease are discussed.

K. E. Halnan

918. Comparative Study of 6-Chloropurine and 6-Mercaptopurine in Acute Leukemia in Adults

R. R. ELLISON, R. T. SILVER, and R. L. ENGLE JR. *Annals of Internal Medicine* [Ann. intern. Med.] 51, 322-338, Aug., 1959. 4 figs., 5 refs.

Preliminary observations on an uncontrolled series of cases of acute leukaemia in adults indicated certain differences between the efficacy of 6-chloropurine (6 CP) and that of 6-mercaptopurine (6 MP) in the treatment of this disease. In an attempt to determine the relative efficacy of the two drugs a comparative study was undertaken, using paired cases.

All patients over 14 years of age with acute leukaemia were initially assessed for their suitability for chemotherapy. Those who had severe haemorrhage, infection, or other evidence of fulminating disease were excluded and treated with steroids. A total of 34 patients were divided into two treatment groups, the parameters of age, total leucocyte count, and history of previous therapy being used in order to ensure homogeneity of the patients given each drug. Of 18 patients given 6 MP, 5 responded, one with a complete remission of symptoms and 4 with partial remission. Of 16 patients given 6 CP, one had a complete remission and 2 had a partial remission.

The over-all survival time of 6½ months from the onset of symptoms was the same as that reported by others in cases of acute leukaemia treated with or without purine analogues. There was no difference in survival time between the two treatment groups in the present series. In patients who had a complete or partial remission with either drug the median survival time was 12 months.

D. G. Adamson

919. Plasma-cell Myeloma. II. Clinical Aspects. [Review Article]

E. F. OSSERMAN. *New England Journal of Medicine* [New Engl. J. Med.] 261, 952-960, Nov. 5, 1959, and 1006-1014, Nov. 12, 1959. Bibliography.

Respiratory System

920. Tracheal Extension in Respiration

R. S. HARRIS. *Thorax [Thorax]* 14, 201-210, Sept., 1959. 13 figs., 28 refs.

In this paper from the Department of Anatomy, University of Bristol, a study is reported of the elasticity of the trachea, the isolated trachea being extended by the application of gradually increasing weights to the carina. Maximum extensibility was found to decrease linearly with age. The significance of this is discussed. It is suggested that greater tracheal descent may be associated with predominantly diaphragmatic respiration in childhood.

In order to determine the importance of tracheal descent in the living the forced inspiratory volume in normal subjects was measured with the head in flexed and extended positions. Head extension reduced the amount the carina could descend and caused a diminution in the forced inspiratory volume by 500 ml. over the first half-second of inspiration and also prolonged the inspiratory phase of forced respiration. The flow rate at the beginning of inspiration was decreased by full head extension, and the author suggests that this may be due to mechanical compression of the trachea or active constriction due to stimulation of stretch receptors.

Strips of tracheal wall from newborn infants were fixed in formol saline in extended and relaxed states and examined histologically. It was found that extension caused compression of the acini of mucous glands and "deformation of the cartilages and their perichondria".

D. Goldman

921. The Solitary Circumscribed Pulmonary Lesion Due to Bronchogenic Carcinoma: a 3-Year Follow-up Study of 94 Surgically Treated Patients

J. W. VANCE, C. A. GOOD, C. H. HODGSON, J. W. KIRK-LIN, and R. P. GAGE. *Diseases of the Chest [Dis. Chest]* 36, 231-237, Sept., 1959. 12 refs.

For 94 surgically treated patients who had bronchogenic carcinoma that presented in the thoracic roentgenogram as a solitary circumscribed pulmonary lesion, the resectability rate was 90% and the hospital mortality rate was 5.3%. Cytologic examination of the sputum appeared to be of definite value in the preoperative diagnosis of the uncalcified solitary pulmonary lesion. The presence or absence of thoracic symptoms seemed to be the most significant prognostic variable studied. The over-all 3-year survival rate based on 93 traced patients was 26.6%. The 3-year survival rate for patients who had excision of all apparent bronchogenic carcinoma was 44.7%. Compared with a previous series reported from this institution [Mayo Clinic], there was no essential difference in the 3-year survival rates for resectable bronchogenic carcinoma whether or not it presented on the thoracic roentgenogram as a solitary circumscribed pulmonary lesion.

Present surgical treatment of bronchogenic carcinoma must be vigorously pursued with a maximal effort directed at early diagnosis and early surgical resection.— [Authors' summary.]

922. Pathological Factors in the Prognosis of Bronchial Carcinoma following Surgical Excision

W. J. HANBURY. *Tubercle [Tubercle (Lond.)]* 40, 257-264, Aug., 1959. 3 figs., 9 refs.

At St. Bartholomew's Hospital, London, the pathological features of tissue obtained at lung resection for bronchial carcinoma in 26 patients surviving 5 years or longer after operation were compared with those in similar tissue from 55 patients operated on during the same period who failed to survive 5 years. Lobectomy was performed in 2 cases in the former group and in 5 in the latter; in all the other cases pneumonectomy was carried out with excision of lymph nodes.

The prognosis was best in cases of squamous-celled carcinoma (present in 24 (92%) of the 5-year survivors compared with 36 (65%) of the non-survivors), in cases in which the growth arose in the left upper lobe, and in cases where there was no extra-pulmonary spread or spread to the regional lymph nodes. (Lymph nodes were involved in 11 (42%) of the 5-year survivors and 42 (76%) of the non-survivors.) There appeared to be no relationship between survival time and the size of the tumour at the time of operation or the degree of mitotic activity of the tumour cells as seen in routine histological sections.

F. J. Sambrook Gowar

923. Patterns of Disturbed Lung Function in Patients with Emphysematous Bullae

C. OGILVIE and M. CATTERALL. *Thorax [Thorax]* 14, 216-224, Sept., 1959. 5 figs., 11 refs.

Lung volume, flow rate, pulmonary diffusing capacity, and maximum pulmonary ventilation were studied in 14 patients with emphysematous bullae at the London Hospital. The findings, together with the clinical and radiological data, enabled the authors to divide the patients into 4 groups as follows. Group 1 included 5 patients with multiple bullae. This group was characterized by minimum bronchitis and disability, but a tendency to spontaneous pneumothorax. Unlike chronic obstructive emphysema, there was an increased residual volume with a normal expiratory flow rate so that the increased volume was not due to bronchial obstruction. Group 2 contained 2 patients with solitary bullae and healthy lungs. Although the bullae were very large, the results of pulmonary function tests were normal. Group 3 included 5 patients with bullae associated with chronic obstructive vesicular emphysema; all suffered from recurrent attacks of disabling bronchitis. The bullae in these cases, in contrast to Group-1 cases, were in the lower lobes. The only difference between the results of

pulmonary function studies in this group and those in cases of non-bullous emphysema was that the increase in residual volume was less in the former. The authors suggest that large bullae could even encourage more efficient ventilation by partial deflation of the over-distended lung. Group 4 consisted of 2 patients with "honeycomb" changes in the lungs and progressive disability. There was increased residual volume without bronchial obstruction, but with a severe degree of alveolo-capillary block.

D. Goldman

924. **Relapses after Corticotherapy of Pulmonary Sarcoidosis and Their Treatment.** (Les rechutes après corticothérapie de la sarcoïdose pulmonaire et leur traitement) J. TURIAT, P. MARLAND, and Y. JEANJEAN. *Revue de tuberculose et de pneumologie [Rev. Tuberc. (Paris)]* 23, 669-684, July [received Oct.], 1959. 6 figs., 12 refs.

There is little doubt that the majority of cases of pulmonary sarcoidosis respond very satisfactorily to corticosteroids and ACTH. Subjective improvement takes place rapidly, and though the lung shadows take longer to regress, this regression is frequently complete. However, radiological breakdown commonly follows cessation of treatment, and in this paper from the Hôpital Bichat, Paris, the authors expound some definite views on this problem, basing these in part on 6 cases of severe pulmonary sarcoidosis which broke down following corticosteroid therapy; brief histories of the 6 cases are presented, with reproductions of radiographs.

From their extensive study of these cases the authors conclude that therapy should be continued for at least 18 months and preferably for 2 years. The initial treatment should be with full dosage and this should be tapered off very gradually. Failure to prolong the therapy for a sufficient length of time will lead only to relapse—in contradistinction to those cases which undergo spontaneous cure, for these never, or scarcely ever, relapse. They state that progress is very satisfactory with corticosteroids even when the drug has been used on a previous occasion for the specific treatment of sarcoidosis.

[The authors make no mention of whether it is desirable or not to "cover" the steroid therapy with antituberculous agents. From a perusal of this paper it would appear to be a common failing in France for certain physicians to diagnose sarcoid as active pulmonary tuberculosis and treat it as such.]

Paul B. Woolley

925. **The Significance of Respiratory Symptoms and the Diagnosis of Chronic Bronchitis in a Working Population**

C. M. FLETCHER, P. C. ELMES, A. S. FAIRBAIRN, and C. H. WOOD. *British Medical Journal [Brit. med. J.]* 2, 257-266, Aug. 29, 1959. 2 figs., 18 refs.

In this survey 192 postmen between the ages of 40 and 59 and 192 women sorters of the same age group employed at the General Post Office in London were investigated by means of a questionnaire (part of which is reproduced) with regard to cough, sputum, and shortness of breath, and 144 of each group by examination of specimens of sputum. Measurements of the one-second

forced expiratory volume were derived from tracings of expirations made on a light spirometer with a paper speed of 2 cm. per second, the results being multiplied by 35 and expressed as the indirect maximum breathing capacity (M.B.C.) since this correction has been most widely used in epidemiological surveys. Sickness absence records of each subject were inspected and all absences lasting more than one week and with a diagnosis of influenza, bronchial catarrh, or bronchitis were considered to be chest illnesses.

Analysis of the results showed that the men had more cough and sputum than the women, but the prevalence of other symptoms and of chest illnesses was similar in the two sexes. The symptoms increased with age in the men, but not in the women, and this difference could not be closely correlated with differences in smoking habits. Unproductive cough was present in only 5 men and 15 women, and none of these showed a significant fall in indirect M.B.C. It is therefore suggested that chronic bronchitis may be defined as "the production of phlegm on most days for at least three months every year" and that it is possible to recognize two grades of chronic bronchitis: (1) that seen in patients who produce phlegm only on getting up in the morning or only later in the day; and (2) that in patients who produce phlegm both on rising and also throughout the day. The relationship between the grade of bronchitis (based on the answers to the questionnaire) on the one hand and the number of bronchitic chest illnesses and impairment of age-standardized indirect M.B.C. on the other among the 144 men was as follows (percentages are given in parentheses).

Symptomatic Grade of Bronchitis	Chest Illnesses			Indirect M.B.C.		
	None	Only One	Two or More	Higher than 1 S.D. Below Mean	1-2 S.D. Below Mean	More than 2 S.D. Below Mean
0	51 (82.5)	7 (11)	4 (6.5)	52 (86)	9 (15)	0
1	34 (74)	5 (11)	7 (15)	36 (78.5)	9 (19.5)	1 (2)
2	17 (47.5)	6 (16.5)	13 (36)	20 (56)	6 (16.5)	10 (27.5)
Total	102 (71)	18 (12.5)	24 (16.5)	108 (76)	24 (16.5)	11 (7.5)
	$\chi^2=17.2$ $P<0.001$			$\chi^2=28.5$ $P<0.001$		

These findings suggest that chronic bronchitis should be diagnosed in subjects with a productive cough not due to other causes and that disability resulting from impairment of ventilatory capacity or recurrent chest illnesses should be regarded as complications and not as essential features of the disease, since it is important to recognize the disease before it has produced permanent disability. The disabling form of the disease can be referred to as "chronic bronchitis with ventilatory impairment" or "chronic bronchitis with recurring exacerbations". Such disability appears to be a less frequent consequence of chronic bronchitis in men than in women.

Kenneth M. A. Perry

Otorhinolaryngology

926. **The Clinical Significance of a Lump in the Throat**
G. E. TREMBLE. *A.M.A. Archives of Otolaryngology*
[*A.M.A. Arch. Otolaryng.*] 70, 157-165, Aug., 1959.
4 figs., 19 refs.

The complaint of "a lump in the throat" is very generally regarded as of "functional origin". Since it is becoming increasingly common owing, as many North American surgeons consider, to the "increasing tension of every-day life", there is a danger of treating the symptom too lightly. The author urges that every such case should be given a thorough examination, including the larynx, base of the tongue, nose and postnasal space, tonsils, and chest. Any difficulty or pain in swallowing suggests a possible organic lesion, but such a lesion may be present when the only abnormal sensation is the "lump".

Mills (*J. Laryng.*, 1956, 70, 530) distinguished 3 types of "functional lump": (1) the lump that moves up and down and is common after an influenza attack; it is caused by friction of the posterior surface of the cricoid against a generally inflamed mucosa; (2) the "lump with aching", which occurs most often in women and is associated with a thin, pallid mucosa or sometimes with thyroid insufficiency; (3) the "emotional lump", seen in subjects with an unstable nervous system, usually under strain and often due to fear of malignancy. Excess of smoking or drinking causes a low-grade chronic inflammation of the mucosa and aggravates the symptoms. Inflamed lateral pharyngeal bands or enlarged lymphoid follicles may contribute to the symptoms, but are not usually the basic cause. Negus (*Laryngoscope*, 1938, 48, 847) associated the feeling of a lump with spasm of the cricopharyngeal sphincter or with a neoplasm in the pyriform fossa or post-cricoid region. In all cases not yielding to treatment radiography and direct examination should be carried out.

[A cause not mentioned by the author, and which is not uncommon, is deformity or abnormality of the cervical vertebrae.]

F. W. Watkyn-Thomas

927. **Costen's Syndrome: a Reinterpretation**
A. S. FREESE. *A.M.A. Archives of Otolaryngology*
[*A.M.A. Arch. Otolaryng.*] 70, 309-314, Sept., 1959.
1 fig., bibliography.

Costen stated in 1934 that over-closure of the mandible caused numerous symptoms, these including: (1) aural signs, such as deafness, tinnitus, and "stiffness"; (2) pains in the head and neck, occipital and vertical headaches, and "pain typical of sinus disease"; and (3) vertigo, burning sensations in the tongue and throat, and a metallic taste in the mouth. He suggested that all these could be cured by "opening the bite". The present author, analysing these signs and symptoms, points out that so far there has been no evidence of any improvement in deafness by "opening the bite". Further he shows that the only possible common ana-

tomical factor in this symptom-complex could be interference with the lymphatics from the inner ear, which pass through the petrotympanic fissure and the tissues of the articular fossa. But he has himself found that elimination of myofascial "trigger regions" about the mandibular joint has occasionally relieved tinnitus and mild deafness, without any alteration of the "bite" being made. Though he has not yet worked this out audiometrically he suggests nevertheless that some muscular spasm may constrict the Eustachian tube. The head and neck pains he regards as being due to stimulation of myofascial "trigger areas" not necessarily in any way connected with the joint, and it is now recognized that postural vertigo can be produced in such a manner.

[In his discussion the author does not mention the importance of eliminating postural factors and minor abnormalities of the cervical vertebrae. Many of these cases can be cured by physiotherapy. Postural vertigo caused by myofascial irritation of the nuchal musculature is not uncommon, and may well be due to interference with the labyrinthine neck reflexes.]

F. W. Watkyn-Thomas

928. **Otogenic Meningitis in Infancy and Childhood in the Antibiotic Era**
H. J. HARA. *A.M.A. Archives of Otolaryngology*
[*A.M.A. Arch. Otolaryng.*] 70, 315-320, Sept., 1959.
3 figs., 14 refs.

The problem of otitic meningitis has not been fully solved, especially in regard to young children. Over the 8-year period 1950-7 the author has treated at Los Angeles County General Hospital 38 cases of purulent otitic meningitis in children under 13 years of age. Of the 19 who were less than 1 year old 12 died, a mortality of 63%; of 4 aged 1 to 2 years 2 (50%) died, but above that age mortality fell sharply. (No cases of tuberculous or chronic meningitis were included in the series.) The high mortality in those under 1 year old is attributed to (1) anatomical factors, the pathways to intracranial infection being still unclosed at this age, (2) the lack of natural immunity, (3) the difficulty in recognizing otoscopic changes in the middle ear, and (4) the altered behaviour of the organisms under inadequate and inappropriate drugs. Of the 9 children in the series who had convulsions only one recovered, while of the 14 who had shown signs of meningitis for 5 or more days before admission 9 (64%) died. In 3 of the fatal cases diarrhoea, vomiting, and dehydration had started before admission and the otitis had been overlooked. In other fatal cases in which nausea and vomiting were initial symptoms the otitis was not suspected before admission. In 2 further cases—one fatal—there had been head injuries; such injuries, even if apparently trivial, may provide a portal of entry for infection. The author emphasizes the value of myringotomy and again comments on the different appearance of the membrane as the result of the action of antibiotics on the infecting

organism. He concludes: "Masking of symptoms of acute otitis media was the chief cause of delay in diagnosis. This in turn contributed to a high mortality rate in this series."

F. W. Watkyn-Thomas

929. An Exploratory Investigation of Delayed Progressive Neural Hypacusis in Children

S. J. BROCKMAN. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **70**, 340-356, Sept., 1959. 18 figs., 12 refs.

Nerve deafness in children is much more common than is usually thought, partly because the possibility is often overlooked now that middle-ear infections are so easily treated with antibiotics. In many cases the deafness—probably congenital or hereditary—is detected within a few months after birth, but there is a group of children who appear to hear normally at first but then, without any obvious causal factor, begin between the ages of 3 and 6 to show deafness of the nerve type, which seems to increase with age.

In this paper from the Children's Hospital, Los Angeles, 14 cases are analysed, 13 in children and one in an adult who was the mother of 2 of the children. The evidence showed (1) steady increase of a "nerve type" of deafness between 4 and 7 years of age; (2) apparent arrest for several years; followed by (3) a further increase in the deafness, most marked in the high tone range. There is a strong probability of increasing deafness in these cases and therefore a need for auditory rehabilitation.

F. W. Watkyn-Thomas

930. Sudden Deafness and Bell's Palsy: a Common Cause

W. H. SAUNDERS and W. H. LIPPY. *Annals of Otolaryngology and Rhinology* [*Ann. Otol. (St Louis)*] **68**, 830-837, Sept., 1959. 2 refs.

At Ohio State University Hospital, Columbus, 9 patients with sudden deafness affecting one ear were examined, and of these 6 showed a positive reaction in the blood serum for mumps. All the patients had a history of mumps in childhood. Of 10 patients with an undisputed Bell's palsy, 4 had a positive serum reaction for mumps. Among a control group of 370 patients only 9 (2.5%) showed a positive serum reaction for mumps.

William McKenzie

931. Experimental Observations on Postural Nystagmus in the Cat

C. FERNANDEZ, R. ALZATE, and J. R. LINDSAY. *Annals of Otolaryngology and Rhinology* [*Ann. Otol. (St Louis)*] **68**, 816-829, Sept., 1959. 17 refs.

The physiological basis of the mechanism which produces postural nystagmus was investigated at the University of Chicago. Section of one utricular nerve produced a nystagmus of the benign paroxysmal type, supporting the suggestion of Hallpike and Dix that the cause of this type of nystagmus lies in a disorder of the utricle. Unilateral labyrinthectomy did not produce postural nystagmus, but postural nystagmus was seen after partial loss of labyrinth function when the nerves to the utricle and the external and superior semicircular

canals were cut. The postural nystagmus may be due to the activity of the remaining vestibular receptors.

Lesions of the flocculonodular lobe of the cerebellum will produce a postural nystagmus of the benign paroxysmal type, but this nystagmus disappears if cocaine is applied to both labyrinths. The authors point out that disappearance of postural nystagmus by surgical destruction of the labyrinth does not mean that positional nystagmus begins in the vestibular sense organ.

William McKenzie

932. The Surgical Treatment of Facial Paralysis and Traumatic Conductive Deafness in Fractures of the Temporal Bone

H. E. MCHUGH. *Annals of Otolaryngology and Rhinology* [*Ann. Otol. (St Louis)*] **68**, 855-889, Sept., 1959. 19 figs., 25 refs.

In cases of closed head injury longitudinal fractures of the temporal bone with damage to the middle ear are more common than transverse fractures, which usually destroy the internal ear. In transverse fractures the facial nerve is often cut and part may be destroyed. In longitudinal fractures facial paralysis occurs in about 15% of cases, and of these 12% recover spontaneously. Signs of recovery appear within 3 weeks in 90% of those recovering spontaneously, and in the remaining 10% signs of recovery are seen within 7 weeks. It is suggested that the facial nerve should be explored if there is no facial movement after 3 weeks and that recovery may be hastened in some cases by exploration before the end of 7 weeks.

William McKenzie

933. Indications for a Submucous Resection

M. SPECTOR. *A.M.A. Archives of Otolaryngology* [*A.M.A. Arch. Otolaryng.*] **70**, 334-339, Sept., 1959. 2 figs., 7 refs.

The operation of submucous resection of a deviated nasal septum, introduced some 50 years ago, was at first used with excessive enthusiasm, but more recently has been regarded with undue suspicion. The author presents what in his view are the proper indications for this operation. In allergic cases resection should be performed only when other methods have failed and clearance of the bony obstruction is needed to assist them to succeed. The patient must be told that resection alone will not cure him and that other treatment will still be needed. In the author's experience a patient with severe asthma and allergy has never been improved by resection. Headache without other nasal complaints is also very seldom relieved. Suitable cases for the operation are those in which a definite obstruction is caused by the deviation, especially when there is an associated sinusitis, repeated upper respiratory infection, and recurrent epistaxis or septal ulceration. In sinusitis the indication is obstruction to drainage by the deviation; in many of these cases surgery of the sinus is required as well. The usual obstructive deviation is a vomerocartilaginous ridge, and this is well described. Outlining his operative technique the author stresses that it is only necessary to remove those portions which actually obstruct.

F. W. Watkyn-Thomas

Urogenital System

934. Recovery of Renal Function after Acute Renal Failure

K. D. G. EDWARDS. *Australasian Annals of Medicine* [Aust. Ann. Med.] 8, 195-199, Aug. [received Oct.], 1959. 2 figs., 7 refs.

At Sidney Hospital, Australia, renal function tests were carried out following severe acute renal failure in 15 patients, 12 of whom had been severely ill, 11 of them having had treatment by dialysis with an artificial kidney. The tests were performed over a follow-up period of 2 to 76 weeks after the onset of diuresis. The duration of oliguria had ranged from 7 to 19 days (average 13.5 days). In the early diuretic phase the blood pressure was above 140/95 mm. Hg in 6 patients, but hypertension persisted in only one. Proteinuria, haematuria, and cylindruria were common in the early diuretic phase and persisted in 2 cases. The endogenous creatinine clearance curve improved during the first 12 weeks after the onset of diuresis and then flattened out in a plateau which was within the normal range in 8 out of 9 cases; in one case, that of a 40-year-old man who had had traumatic shock, it remained at half the normal value after 17 weeks. In all the remaining 6 cases the results of urea clearance tests showed complete recovery of normal renal function.

K. G. Lowe

935. Pathogenesis of Traumatic Uraemia: a Revised Concept

S. SEVITT. *Lancet* [Lancet] 2, 135-141, Aug. 22, 1959. 7 figs., 44 refs.

The pathogenesis of post-traumatic renal failure and uraemia is discussed in this paper from the Birmingham Accident Hospital and it is suggested that a persistent and often irreversible fall in the glomerular filtration rate due to renal vasoconstriction is the basic cause, rather than tubular necrosis with back diffusion of the filtrate through damaged tubules, for the following reasons. (1) Acute renal failure after injury cannot satisfactorily be explained by tubular damage alone; thus uraemia without oliguria could not result solely from tubular dysfunction. Also, urine in both oliguric and non-oliguric cases contains much potassium but little sodium and chloride. Such an electrolyte pattern could not result from tubular damage, but only from a tubular response to the adrenocortical excretion of aldosterone as the reaction to "stress". Further, severe tubular failure would allow the appearance of glycosuria, but this does not occur. (2) It is known that tubular necrosis can occur without renal failure and vice versa. Their common association in the present condition is probably due to their common cause, namely, the renal vasoconstriction. (3) Finally, hyperkalaemia, hypocalcaemia, and acidosis from failure to excrete hydrogen ion result from severe oliguria, but not from tubular necrosis. These conditions are not seen in cases of uraemia with-

out oliguria, although in the latter tubular necrosis is present.

It is concluded that the explanation that the demonstrable renal vasoconstriction and consequent decrease in renal blood flow result in a fall in the glomerular filtration rate (G.F.R.) best satisfies the findings. The fact that the fall in the G.F.R. is greater than the fall in renal blood flow suggests that there may be additional secondary glomerular changes. Haem compounds may also contribute to produce vasoconstriction. The rate of urine flow then depends on a balance between a diminished G.F.R. and a diminished tubular reabsorption. Oliguria results when the diminution in reabsorption is insufficient to compensate for a grossly diminished G.F.R., the result of this then being retention of water, potassium, hydrogen ions, and phosphate causing the observed hyperkalaemia and hyperphosphataemia (and thereby hypocalcaemia) and acidosis as well as azotaemia.

David Phear

936. Vaccinal Nephropathies (Combined T.A.B.-Diphtheria-Tetanus Vaccine). (Néphropathies vaccinales (vaccin TABDT))

J. G. BERNARD, J. LAABAN, and S. LECHAT. *Presse médicale* [Presse méd.] 67, 1511-1513, Aug. 22, 1959. 1 ref.

Triple vaccination against typhoid and paratyphoid A and B, diphtheria, and tetanus was made compulsory in the French Army in 1936. This report from Val-de-Grâce Military Hospital, Paris, describes 33 cases observed between 1952 and 1958 in which renal complications followed such vaccination. The actual incidence is unknown, but it appears to be much lower than the 1.3% suggested in 1937.

The cases fell into two main groups. (1) In 15 cases the onset occurred within a few hours of the first injection; 6 of the patients complained of lumbar pain, while other symptoms were fever, rigors, headache, and some degree of "shock". Haematuria was present in 5 cases, albuminuria in 7, and albuminuria and increased number of cells in the urine in 3; one patient had hypertension and oedema. The prognosis in this group was good, only one case being found abnormal 2 years later, when there was hypertension and inconsistent albuminuria. (2) In the second group, consisting of 18 cases, the onset was insidious, the first sign being the discovery of albuminuria when the urine was tested before the next injection of vaccine. In 9 cases this followed the first injection, in 5 the second injection, and in 4 the third or subsequent injections. In 7 cases the urine contained granular casts and one patient had hypertension and oedema. The prognosis in this group was less good, one patient dying four years later from chronic nephritis, while in half the cases some renal abnormality persisted.

It appeared that some of these illnesses might have been due to intercurrent throat infections, and in others there was evidence of antecedent renal disease. Subsequent tests revealed skin hypersensitivity to TAB or diphtheria toxin in 9 cases, the skin tests in 2 being followed by an increase in microscopic haematuria. No case of hypersensitivity to tetanus toxoid was found. Rare as this complication is, it is suggested that vaccination against typhoid or diphtheria is contraindicated in individuals with a history of nephritis or with a history of allergic illness.

C. Bruce Perry

937. Salt-wasting Renal Disease: Metabolic Observations on a Patient with "Salt-losing Nephritis"

S. W. STANBURY and R. F. MAHLER. *Quarterly Journal of Medicine [Quart. J. Med.]* 28, 425-447, July [received Sept.], 1959. 8 figs., bibliography.

From the results of detailed metabolic studies carried out on a patient with salt-losing renal failure the authors of this paper from Manchester Royal Infirmary consider that this syndrome is simply a "caricature" of ordinary renal failure and not an entity in itself. Deprivation of dietary sodium caused lassitude, anorexia, nausea, and hypotension; the volume of urine declined and the sodium loss decreased almost to the level of dietary intake. A catabolic reaction took place and the serum levels of potassium and urea rose. The renal capacity to vary the output of potassium was impaired. Replacement of sodium produced a diuresis and a fall in blood urea level. Urinary excretion of aldosterone was greatly increased during the phase of sodium depletion, and this increase persisted long after the sodium depletion was corrected.

It is suggested that in renal failure an osmotic diuresis is constantly operating since an abnormally heavy solute load is delivered to each surviving nephron. This osmotic diuresis reduces the reabsorption of sodium and chloride. After the therapeutic administration of sodium salts the solute load is increased still more, causing further diuresis (per individual nephron, if not in total volume) and reduction in the body content of urea.

T. B. Begg

938. Focal Glomerulonephritis: a Study Based on Renal Biopsies

R. H. HEPTINSTALL and A. M. JOEKES. *Quarterly Journal of Medicine [Quart. J. Med.]* 28, 329-346, July [received Sept.], 1959. 8 figs., 26 refs.

The authors, working at St. Mary's Hospital, London, studied 13 cases of focal glomerulonephritis which were diagnosed on examination of renal biopsy tissue obtained from a total of 100 cases of various forms of renal disease. Classically, focal glomerulonephritis is said to be characterized by haematuria and proteinuria, usually occurring at the height of an infection.

The commonest clinical picture in this series referable to the renal involvement resembled that of Type-I acute glomerulonephritis described by Ellis, with oedema, hypertension, haematuria, and nitrogen retention. Heavy proteinuria often persisted for many weeks and

5 patients showed a transient nephrotic syndrome. Proteinuria occurred in all cases and haematuria in 10. There was a striking association with conditions commonly regarded as due to sensitization. The series included 2 cases of proven and one of probable systemic lupus erythematosus and 3 clear and 2 doubtful cases of the Schönlein-Henoch syndrome. One patient had primary pulmonary haemosiderosis and another probably had periarteritis nodosa. In 7 cases an infection preceded the onset of renal involvement. During a short follow-up period one patient with systemic lupus erythematosus developed hypertension, while 3 of the 7 patients who were initially hypertensive became normotensive.

Histological examination showed that one-quarter to two-thirds of the glomeruli were abnormal. Localized or diffuse proliferation of the endothelial and epithelial cells of the glomerular tufts was prominent. In some cases adhesions between the tuft and Bowman's capsule, glomerular necrosis, intracapillary thrombosis, and thickening of the basement membrane were observed. Some glomeruli showed gross fibrosis or hyalinization. Vascular changes were insignificant.

The authors discuss the similarity histologically between these cases, the focal embolic nephritis of subacute bacterial endocarditis, and focal nephritis of periarteritis nodosa of the so-called microscopic type. They consider that focal glomerulonephritis is clinically and histologically distinct from Ellis's Type-I acute glomerulonephritis.

G. L. Asherson

939. Artificial Kidney in the Treatment of Uremia Associated with Acute Glomerulonephritis (with a Note on Regional Heparinization)

A. ANDERSON and W. J. KOLFF. *Annals of Internal Medicine [Ann. intern. Med.]* 51, 476-487, Sept., 1959. 3 figs., 35 refs.

In this paper from the Cleveland Clinic, Ohio, the authors describe the use of a disposable twin-coil artificial kidney in the treatment of 4 patients (2 adults and 2 children) with acute glomerulonephritis and uraemia. By increasing the hydrostatic pressure in the coils to 280 mm. Hg 4 to 5 litres of ultrafiltrate could be removed during a 6-hour dialysis. Of the 4 patients, 2 underwent dialysis on one occasion and one patient on two occasions; all 3 recovered. The remaining patient, an adult, died in cardiac failure during the fourth dialysis. The indications for dialysis in the children were potassium intoxication and severe acidosis; the indications in the adults were clinical and chemical, both patients being stuporose, overhydrated, and hypertensive, with severe chemical derangement. To protect the patient from the dangers of systemic heparin a method of "regional heparinization" was used, in which heparin was introduced into the inflow tube of the artificial kidney and protamine sulphate into the outflow tube. A rise in blood pressure during dialysis was controlled by removing blood from the circulation or by intravenous administration of ganglion-blocking agents. Pulmonary oedema was rapidly eliminated by ultrafiltration with the artificial kidney.

C. Bruce Perry

Endocrinology

THYROID GLAND

940. Bone Changes in Adult Cretins

I. B. D. MIDDLEMASS. *British Journal of Radiology* [Brit. J. Radiol.] 32, 685-688, Oct., 1959. 3 figs., 6 refs.

Twelve out of 32 untreated or inadequately treated adult cretins showed no skeletal abnormalities in the skull, lumbar spine, hips or wrists, except for the smallness of their bones. In the remaining patients findings of interest were absent frontal sinuses (but normal maxillary antra) in 15, considerable enlargement of the pituitary fossa in 6, deformity of the dorso-lumbar spine in 4, fragmentation and flattening of the femoral heads in 2, flattening of more normally ossified femoral heads in one and unilateral C.D.H. in 2. Multiple abnormalities were present in some of the more severe cases.—[Author's summary.]

941. The Nature and Prognosis of Heart Disease in Thyrotoxicosis: a Review of 150 Patients Treated with ^{131}I

G. SANDLER and G. M. WILSON. *Quarterly Journal of Medicine* [Quart. J. Med.] 28, 347-369, July [received Sept.], 1959. 8 figs., bibliography.

Evidence of heart disease was present in 150 out of 462 thyrotoxic patients treated with radioactive iodine [^{131}I] at Sheffield between 1949 and 1956. Eighty-six of these patients had associated heart disease, comprising ischaemic, hypertensive, rheumatic, pulmonary, and congenital heart disease. The remaining 64 patients had auricular fibrillation, congestive cardiac failure, or cardiomegaly alone, in the absence of any clinical, radiological, or electrocardiographic evidence of associated heart disease. Thyrotoxic patients with cardiac involvement were found in the older age groups. Sex, incidence of goitre, and severity and duration of thyrotoxicosis did not appear to be related to the incidence of cardiac involvement.

Approximately one-third of the patients with auricular fibrillation reverted spontaneously to normal rhythm after ^{131}I therapy, the most important factor adversely influencing reversion being the presence of congestive failure. The rate of reversion was higher in younger patients and male patients. More than half of the patients with congestive cardiac failure had no further attacks of failure after ^{131}I therapy, and more than one-third required no further treatment with digitalis or mersalyl. The prognosis in patients with congestive failure and auricular fibrillation was more favourable if sinus rhythm was restored. In 13 patients without associated heart disease there was radiological and electrocardiographic evidence of left ventricular enlargement in the absence of auricular fibrillation and congestive cardiac failure. A return to normal did not occur after ^{131}I therapy.

Post-mortem findings in 9 patients in the series are discussed. In 4 of these cases no cause of heart failure

other than thyrotoxicosis was found. The role of thyrotoxicosis alone in causing heart disease, and the importance of undetected coronary artery disease and masked hypertension, are considered. It is concluded that although thyrotoxicosis may not be the sole cause of the cardiac disability, in many patients with thyrotoxicosis and heart disease it is nevertheless the predominant factor. ^{131}I therapy is safe and effective, and is the treatment of choice in thyrotoxic patients with severe cardiac complications.—[Authors' summary.]

942. A Correlation of Clinical and Hemodynamic Studies in Patients with Hyperthyroidism With and Without Congestive Heart Failure

J. S. GRAETTINGER, J. J. MUENSTER, L. A. SILVERSTONE, and J. A. CAMPBELL. *Journal of Clinical Investigation* [J. clin. Invest.] 38, 1316-1327, Aug., 1959. Bibliography.

A study of the various haemodynamic indices in 21 hyperthyroid patients with and without congestive failure was made at the Presbyterian Hospital (University of Illinois College of Medicine), Chicago. Of the 14 patients without congestive failure, 6 had antecedent heart disease, and of the 7 with congestive failure, 4 had antecedent heart disease. The haemodynamic factors investigated included cardiac output, arterio-venous oxygen difference, right atrial and mean pulmonary arterial pressure, pulmonary and systemic resistance, and left ventricular work index.

The patients with no heart disease or congestive failure had an abnormally high mean cardiac index, but responded to mild exercise normally with an increase in cardiac output and a fall in systemic resistance and without change in right atrial or pulmonary arterial pressure. Patients with associated heart disease but without congestive failure also showed an elevated resting cardiac index and a normal increase in cardiac output on exercise, but developed a significant increase in right atrial pressure on exertion, while systemic resistance did not change; this is regarded as indicating slight impairment of cardiac function. Among the 7 patients with congestive failure, 4 had a normal resting cardiac output. In these patients exercise failed to produce an increase in cardiac output, but resulted in an increase in right atrial and pulmonary arterial pressure, the systemic resistance remaining unchanged; 3 patients in this group had antecedent heart disease. In the remaining 3 patients with congestive failure the resting cardiac output and right atrial pressure were elevated and systemic resistance reduced, and exercise produced a fall in the cardiac index and a further increase in right atrial pressure; one of these 3 patients had antecedent heart disease.

The authors review the possible aetiological factors in the production of congestive failure in hyperthyroidism in the light of this study. These include a direct altera-

tion of myocardial metabolism by thyroxine (possibly mediated through the sympathetic nervous system), the development of atrial fibrillation, the effect of an increased peripheral circulatory load resulting from increased tissue oxygen and heat loss requirements, increase in blood volume, and finally the deleterious effect of unrelated antecedent heart disease on myocardial function. They conclude that any or all of these mechanisms can result in congestive failure in thyrotoxicosis and point out that decompensation can occur in an apparently normal heart from hyperthyroidism alone.

Gerald Sandler

943. Antithyroid Activity Elicited by the Ingestion of Pure Progoitrin, a Naturally Occurring Thioglycoside of the Turnip Family

M. A. GREER and J. M. DEENEY. *Journal of Clinical Investigation* [J. clin. Invest.] 38, 1465-1474, Sept., 1959. 7 figs., 11 refs.

It is known that certain foodstuffs, especially rutabaga and turnip, are goitrogenic. The antithyroid principle is 1:5-vinyl-2-thio-oxazolidone or goitrin, which does not exist in the free state but as a precursor, progoitrin, from which it can be liberated by the action of the enzyme myrosin contained in crucifers. Hitherto it has been thought that cooking denatures this enzyme and so prevents active goitrin from being formed.

At the University of Oregon Medical School, Portland, the authors have re-examined this hypothesis in experiments on both man and rats using crystalline progoitrin prepared from a 75% acetone extract of ground rutabaga or kale seed. Goitrin, which has a maximum specific absorption at 240 m μ compared with 227 m μ for progoitrin, was assayed in biological fluids by means of a Beckman spectrophotometer. Radioactive iodine was used in estimating antithyroid activity. In one thyrotoxic and 7 euthyroid individuals inhibition of ^{131}I uptake was produced by the oral administration of 0.5 to 2 g. of progoitrin, and prior incubation of the progoitrin with myrosin or the addition of the enzyme at the time of giving the progoitrin did not materially affect the results. The antithyroid effect was just as marked in the thyrotoxic as in the euthyroid patients. In one patient with hyperthyroidism a gratifying clinical response was produced by the administration of 1 g. of progoitrin daily. It was found possible to detect goitrin in blood and urine, but only if at least 1.5 g. of progoitrin had been given.

In order to investigate the site of hydrolysis of progoitrin and to determine whether absorption could take place in the colon 4 g. of progoitrin dissolved in saline was given by rectal tube to 3 patients. In 2 cases goitrin was subsequently found in the urine, and in one of these it was also found in the blood. In one subject who had previously received progoitrin by mouth rectal administration of the drug produced a much smaller excretion of goitrin in the urine. Studies in the rat showed that progoitrin produced an antithyroid effect when administered orally, subcutaneously, or intraperitoneally, but in general the drug was most effective when given by mouth.

The authors conclude that since hydrolysis of progoitrin occurs within the body in the absence of exogenous myrosin, it cannot be assumed that cooking will destroy the antithyroid effects of goitrogenic foodstuffs.

D. G. Adamson

944. Clinical and Metabolic Studies in Thyroid Disease. (Lumleian Lectures for 1959)

E. J. WAYNE. *British Medical Journal* [Brit. med. J.] 1, 1-11, Jan. 2, 1960, and 78-90, Jan. 9, 1960. 19 figs., bibliography.

945. A Dissociation of Thyroid Hormonal Effects by Structural Alterations of the Thyroxine Molecule

R. W. RAWSON, W. L. MONEY, R. L. KROC, S. KUMAOKA, R. S. BENUA, and R. D. LEEPER. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 238, 261-273, Sept., 1959. 7 figs., 16 refs.

In view of reports that certain metabolites of thyroxine and triiodothyronine differ qualitatively as well as quantitatively in their physiological effects the authors, working at the Sloan-Kettering Institute and the Memorial Hospital, New York, have studied the activity of more than 60 different analogues of thyroxine both *in vitro* and *in vivo*. They now report comparative studies of eight of these substances: L-thyroxine; 3:5:3'-triiodo-L-thyronine; 3:3':5'-triiodo-DL-thyronine; 3:5:3':5'-tetraiodothyropropionic acid; 3:5:3':5'-triiodothyropropionic acid; 3:5:3':5'-tetraiodothyroacetic acid ("tetrac"); 3:5:3'-triiodothyroacetic acid ("triac"); and Compound 46.

The physiological functions which were measured were: the ability to promote metamorphosis of the tadpole; the suppressive effect on thyroid uptake of ^{131}I in iodine-deficient rats; the ability to prevent goitre formation in rats receiving thiouracil; the metabolism-stimulating function as measured by oxygen consumption; and the ability to suppress the growth of a particular pituitary tumour in hypothyroid mice. The results confirm that there is a striking variation in the physiological effects of the different substances. For example, 3:5:3'-triiodo-L-thyronine is 3 to 8 times more active than thyroxine except in inhibiting the growth of the pituitary tumour, in which respect the two analogues are equally active. Tetrac and triac are more active than thyroxine in promoting metamorphosis, but have only 10% and 20% respectively of the activity of thyroxine in stimulating metabolism.

Comparison of the acute effects of intravenously administered 3:5:3'-triiodothyropropionic acid and 3:5:3'-triiodo-L-thyronine suggested that the former had less than 2% of the calorogenic activity of the latter, but that their abilities to reduce the serum cholesterol level were less disparate. Administration of triiodothyropropionic acid for several weeks to hypothyroid patients in doses which produced a fall in the serum cholesterol level did not alter the rate of oxygen consumption. This substance also produced a fall in the serum cholesterol level in euthyroid patients with hypercholesterolaemia and angina pectoris without causing any increase in symptoms.

Many other examples of the dissociation of the various actions of thyroid hormones are given, and the possible pharmacological value of certain of the analogues is pointed out.

H.-J. B. Galbraith

ADRENAL GLANDS

946. Increased Urinary Excretion of Catechol Amines in the Absence of Known Chromaffin Tumors: a Survey by the Rabbit Aortic-strip Method of 802 Unselected, Hospitalized Patients

R. W. EWER, J. A. ARKINS, B. T. HEFFERNAN, and E. J. LENNON. *Journal of Clinical Endocrinology and Metabolism* [J. clin. Endocr.] 19, 1037-1048, Sept., 1959. 3 figs., 12 refs.

The urinary excretion of catechol amines possessing biological adrenaline and noradrenaline activity was studied at the Milwaukee County Hospital (Marquette University School of Medicine), Wisconsin, the primary aim of the study being to investigate the value of the rabbit aortic-strip method of assay as a screening test for pheochromocytoma. The specimens of urine were added to a bath containing a fresh spiral strip of rabbit aorta and the subsequent contraction in this strip compared with that produced by a standard noradrenaline solution.

In 10 healthy medical students the mean urinary excretion of such catechol amines was $6.05 \mu\text{g.}$ of noradrenaline equivalents (N.E.) per hour (range 1.9 to $10.8 \mu\text{g.}$). Of 802 unselected hospital patients, 37 showed an excretion of $12 \mu\text{g.}$ N.E. per hour or more. Many of these had advanced liver disease, a psychosis, an infection, or a combination of these factors, and several died shortly after the investigation. While an isolated finding of such increased excretion does not provide prima facie evidence of the presence of a pheochromocytoma, it is concluded nevertheless that the method provides a useful screening test for this tumour, provided always that the total clinical situation is taken into account.

David Phear

947. Steroid Therapy in Hirsutism and Virilism

R. R. DE MOWBRAY, A. W. SPENCE, V. C. MEDVEI, and A. M. ROBINSON. *British Medical Journal* [Brit. med. J.] 2, 456-459, Sept. 19, 1959. 4 figs., 3 refs.

The effects of steroid therapy on adrenal virilism with increased excretion of 17-ketosteroids were studied in 8 patients at St. Bartholomew's Hospital, London, the drugs tried being prednisone and prednisolone by mouth, hydrocortisone acetate by intramuscular injection, and prednisolone trimethylacetate, a microcrystalline suspension of the hormone, also by intramuscular injection.

Prednisolone trimethylacetate was given to 5 patients, 4 of whom were hirsute females with oligomenorrhoea and one a female pseudohermaphrodite aged 15 years. The urinary 17-ketosteroid excretion was measured over at least two 24-hour periods, after which one or more intramuscular injections of 200 or 400 mg. of prednisolone trimethylacetate were administered. A fall in the 17-ketosteroid excretion was observed in 3 of the

4 hirsute females with a 400-mg. dose of prednisolone trimethylacetate, but in the pseudohermaphrodite it was necessary to give 400 mg. at weekly intervals to maintain the 24-hour 17-ketosteroid output below 8 mg. In this case suppression continued for as long as 5 months after treatment was discontinued, the total daily excretion amounting to only 1 mg. at one stage.

In 3 patients receiving 20 mg. of prednisone or prednisolone by mouth daily there was an immediate and profound depression of 17-ketosteroid excretion. Steroid therapy was gradually withdrawn over 4 to 7 weeks and was followed by some degree of depression for many weeks thereafter. One hirsute patient, aged 28, with regular menses was given two intramuscular injections each of 250 mg. of hydrocortisone acetate at intervals of one week. The 17-ketosteroid output gradually fell and was still below the control level 43 weeks later. In a second patient given an injection of 250 mg. of hydrocortisone acetate followed by an injection of 125 mg. 2 weeks later and one of 250 mg. after a further 2 weeks 17-ketosteroid excretion had returned to the resting level 6 weeks after the last injection.

The hirsutism was unaffected by steroid therapy. In 2 patients with oligomenorrhoea regular menses were restored, but in one patient with amenorrhoea the condition persisted in spite of prolonged treatment with prednisone. In the remaining patients the menses were normal.

Prednisolone trimethylacetate intramuscularly seemed to be less reliable than prednisolone by mouth, even when given in doses of 400 mg., possibly because of slow absorption. The authors emphasize that adrenocortical function may be suppressed for many weeks or months after withdrawal of therapy, even to a dangerous degree as in one of the cases in the series.

Norval Taylor

DIABETES MELLITUS

948. Hypophysectomy as a Therapeutic Method for Proliferative Diabetic Retinopathy

S. VANNAS, C. A. HERNBERG, and G. AF BJÖRKSTEN. *A.M.A. Archives of Ophthalmology* [A.M.A. Arch. Ophthalm.] 62, 370-380, Sept., 1959. 12 figs., 27 refs.

Proliferative diabetic retinopathy is associated with, and may be due to, overactivity of the adrenal cortex. Alternatively both the diabetes and the retinopathy may be due primarily to some pituitary abnormality of which the adrenocortical hyperfunction is a secondary effect. In either case removal of the pituitary should, theoretically, be beneficial. About 60 cases in which this operation has been performed have so far been reported from various parts of the world, but all except the first have been treated within the last 9 years so that a true assessment of its effectiveness is still not possible.

The present report concerns 10 patients who had had labile diabetes for 10 to 18 years and in whom one eye was severely affected but the other, in most cases, only slightly so. At operation the optic nerve of the worse eye was divided in 8 of the cases for technical reasons. One patient died of a cerebral abscess $3\frac{1}{2}$ months after

operation. The rest were alive after a follow-up period of 3 to 34 months. After operation the diabetes was easier to control and there was evidence that nephropathy did not progress, or even improved. Vision remained unchanged or became better in 7 cases and fundus changes in general improved—in one or two cases [which are well illustrated by photographs] markedly so. Haemorrhages for the most part were absorbed and there were recurrences in only 2 cases; exudates were gradually absorbed and venous changes and retinal oedema also regressed; proliferative changes were more resistant.

With one or two exceptions those who have tried this method of treatment consider that hypophysectomy has a beneficial effect upon diabetic retinopathy. This is the opinion of the present authors, but they emphasize the risks involved and conclude that "it is not yet possible to make a final evaluation" of the operation.

A. Lister

949. Mechanism of Action of Oral Anti-diabetic Drugs

R. AIMAN and N. CHAUDHARY. *British Journal of Pharmacology and Chemotherapy* [Brit. J. Pharmacol.] 14, 377-379, Sept., 1959. 1 fig., 11 refs.

Carbutamide exerted a significant hypoglycaemic action when administered to alloxan-diabetic rabbits maintained with insulin 24 hours after an injection of insulin. No such effect was produced if the drug was given 72 hours after the insulin. It is therefore postulated that carbutamide acts by releasing insulin bound to the plasma proteins.

F. W. Chattaway

950. Chlorpropamide in the Management of Diabetes

S. J. N. SUGAR, L. J. THOMAS, and T. M. EUGENIO. *A.M.A. Archives of Internal Medicine* [A.M.A. Arch. intern. Med.] 104, 360-364, Sept., 1959. 4 figs., 3 refs.

The effect of the sulphonamide derivative chlorpropamide in the control of diabetes was investigated in 84 patients at Prince Georges General Hospital, Cheverly, Maryland, and the District of Columbia General Hospital, Washington, D.C. The patients included 37 previously treated with insulin or by diet alone and 47 whose diabetes was inadequately controlled by tolbutamide. Chlorpropamide was given by mouth in daily doses of 0.5 to 2.5 g., and the control of diabetes was considered satisfactory when the average daily fasting blood sugar level was 200 mg. per 100 ml. or less and the urine contained less than 0.25% sugar. The period of treatment ranged from 2 to 11 months, the majority of the patients being treated as out-patients.

Satisfactory control with chlorpropamide was obtained in 52 (62%) of the patients. Detailed analysis of the results shows that control was successful in 27 (73%) of the 37 patients formerly treated with insulin or by diet alone, in only 2 (20%) of 10 patients who were resistant to tolbutamide from the start, and in 23 (62%) of 37 patients who had at first been treated successfully with tolbutamide, but who had later become unresponsive to that drug. In several cases there was a progressive slow fall in the blood sugar level over several months of treatment with chlorpropamide in spite of a concomitant reduction of dosage, suggesting a cumulative effect.

Side-effects included anorexia, nausea, epigastric pain, generalized muscular weakness (not related to serum potassium changes), skin rashes, leucopenia (one case only), and thyroid depression. These side-effects were probably related to high dosage.

The authors conclude that chlorpropamide is a more potent antidiabetic drug than tolbutamide and gives the best results in middle-aged patients with diabetes of less than 10 years' duration whose insulin requirement is less than 40 units daily. They recommend an initial dosage of 0.25 to 0.5 g. daily.

Gerald Sandler

951. Preliminary Observations on Phenethyldiguanide

R. S. WALKER. *British Medical Journal* [Brit. med. J.] 2, 405-406, Sept. 12, 1959. 8 refs.

A trial of phenethyldiguanide (D.B.I.) in the treatment of 52 diabetic patients attending the out-patient diabetic clinic at Strathclyde Hospital, Motherwell, Scotland, is reported. This substance, unlike the sulphonylureas, is able to influence peripheral glucose utilization and to cause hypoglycaemia in eviscerated animals. The maximum dose of D.B.I. employed was 200 mg. daily, given in divided doses, the patients remaining on their diabetic diet which contained some 170 g. of carbohydrates. The drug was successful (that is, insulin could be withdrawn or was not required to obtain control) in 21 (88%) of 24 adult stable diabetics and in 4 (50%) of 8 stable juvenile diabetics. Like the sulphonylureas, in spite of its different mode of action, D.B.I. is unsuitable for unstable cases of adult or juvenile diabetes. It will control some cases which do not respond to carbutamide. Toxic effects were absent; nausea, when present, was easily overcome and caused no problem in the administration of the drug.

A. I. Suchett-Kaye

952. Resistance to Insulin Due to Neutralizing Antibodies

C. EZRIN and P. J. MOLONEY. *Journal of Clinical Endocrinology and Metabolism* [J. clin. Endocr.] 19, 1055-1068, Sept., 1959. 27 refs.

From the University of Toronto the authors describe in detail a case of insulin-resistant diabetes in a negro woman aged 62 who had previously taken insulin sporadically and was admitted to Toronto General Hospital for control of her diabetes. Shortly after restarting insulin she became extremely resistant to ox, pig, and sheep insulins. The high blood sugar level was unaffected by the administration of 2,100 units of ox insulin (1,000 units of it given intravenously) in one day. Resistance was thought to be due to antibody formation because of the appearance of urticaria, eosinophilia, and anaphylaxis following intravenous insulin injection. Also, the neutralizing factor was present in the serum globulin fraction and insulin could be recovered from neutral insulin-anti-insulin mixtures, indicating that neutralization was not due to enzymic destruction of insulin.

In animal tests it was shown that the neutralizing antibody protected starving mice against convulsions induced by insulins from a large variety of animal

species, except that from guinea-pigs. In the patient no decrease in insulin resistance was produced by giving prednisone, but her diabetes was controlled by means of a low-calorie, high-fat diet, indicating that some endogenous insulin was being secreted and not neutralized. Serum insulin-neutralizing activity was demonstrated in sera from 6 other insulin-resistant cases studied.

David Phear

953. Hypoglycemic Insulin Reactions without Warning Symptoms

M. C. BALODIMOS and H. F. ROOT. *Journal of the American Medical Association [J. Amer. med. Ass.]* **171**, 261-266, Sept. 19, 1959. 16 refs.

From the Joslin Clinic and New England Deaconess Hospital, Boston, the authors report a series of 116 diabetic patients in whom attacks of sudden unconsciousness or serious mental confusion occur as a result of hypoglycaemia due to insulin, but without the usual warning symptoms. No clear relation between the type of insulin employed and the peculiar character of these reactions could be demonstrated. No excessively low blood sugar levels were found, values of 40 to 60 mg. per 100 ml. being recorded in most cases during the reaction. Some of these patients have also experienced reactions in which the normal warning symptoms occur. The explanation of the absence of warning symptoms is still unknown. Prevention includes adjustment of insulin dosage, giving long-acting insulin in the early part of the day and, usually, short-acting insulin for the later dose, and a diet which includes frequent snacks between meals.

A. I. Suchett-Kaye

954. Peripheral Glucose Metabolism in Fasting Control Subjects and Diabetic Patients

W. J. H. BUTTERFIELD and H. E. HOLLING. *Clinical Science [Clin. Sci.]* **18**, 147-174, May [received Sept.], 1959. 12 figs., 33 refs.

Since the blood flow through the tissues is variable, even in the resting state, reported values for uptake of glucose based solely on the estimation of differences in arterio-venous or capillary-venous blood sugar levels may be of limited value. At the M.R.C. Clinical Research Unit, Guy's Hospital, London, the uptake of glucose by forearm tissues, mainly muscle, was calculated from arterial and venous blood sugar levels and from simultaneous measurements of blood flow. The various sources of error concerned in such measurements, including those of the modification of the method of Harding and Down used by the authors as described by King and Wootton (*Micro-analysis in Biochemistry*, London, 1956), are discussed in 3 appendices to the paper. The study was carried out on 6 normal subjects, 4 patients with stable diabetes, 5 with severe diabetes, and 3 with "brittle" diabetes, all in the fasting state.

Except in the cases of "brittle" diabetes the arterial blood sugar level was relatively stable, but blood flow in the forearm was found to be very variable in all subjects. The difference in arterio-venous blood sugar levels was usually positive in normal subjects and stable diabetic patients, occasionally negative in those with

brittle diabetes, and usually negative in the patients with severe diabetes, the results in this last group differing significantly from those in the other groups. It was demonstrated that there was a "threshold" level of blood sugar above which glucose entered the tissues from the blood and below which glucose passed into the blood from the tissues, the latter circumstance being generally found in the cases of severe diabetes with glycosuria. It was also shown that the rate of movement of glucose into and out of the tissues was proportional to the difference between the arterial blood sugar level and the "threshold" value and that the latter was lowered by administration of insulin. The findings are fully discussed.

F. W. Chattaway

955. Assay of Insulin-like Activity in the Plasma of Normal and Diabetic Human Subjects

C. W. BAIRD and J. BORNSTEIN. *Journal of Endocrinology [J. Endocr.]* **19**, 74-80, 1959. 1 fig., 18 refs.

From the University of Melbourne a micro-assay method is described for determining the insulin-like activity of plasma in which, in order to remove the effect of insulin antagonists, the plasma is first extracted with an acid ethanol-*n*-butanol-toluene mixture; insulin activity is then measured by the fall produced in the blood glucose level of adrenalectomized, alloxan-diabetic mice anaesthetized with pentobarbitone, the effect of each extract being compared with that of a standard insulin preparation in a comparable group of mice. It was demonstrated that the rate of recovery of insulin added to plasma was 75%. Application of the method showed that in normal subjects the insulin activity increases with increased ingestion of carbohydrate and that diabetic patients appear to fall into two different groups—those with and those without circulating insulin in their plasma. The authors emphasize, however, the limitations of this technique in the clinical study of diabetes mellitus.

F. W. Chattaway

956. Incidence of Peptic Ulcer in Diabetes Mellitus. [In English]

G. DOTEVALL. *Acta medica Scandinavica [Acta. med. scand.]* **164**, 463-477, 1959. 1 fig., 45 refs.

Among a total of 1,218 diabetics who had been treated at Centrallasarettet, Halmstad, and at Länsallasarettet, Varberg, Sweden, the author found 22 cases of peptic ulcer (1.8%). The incidence of gastric ulcer was virtually normal, but the number of cases of duodenal ulcer (9) was much lower than the expected number of 32.7. If only patients with diabetes of more than 15 years' duration were considered, however, the observed number for duodenal ulcer approximated to that expected. The author suggests that this reduced incidence of duodenal ulcer might be related to the known high incidence of hypochylia in diabetes, thought to be caused by hyperglycaemia, or alternatively to the reduced adrenocortical activity which occurs in diabetes. The increased frequency of ulcers in patients with long-standing diabetes was considered to reflect the high incidence of associated vascular disease.

A. Gordon Beckett

The Rheumatic Diseases

957. **Serum Glycoproteins in Rheumatic Fever and in the Active Phase of Rheumatoid Arthritis.** (Le glicoproteine del siero nel reumatismo articolare acuto e nell'artrite reumatoide in fase attiva)

L. BUSCARINI and G. BARONCELLI. *Progresso medico* [Progr. med. (Napoli)] 15, 528-535, Sept. 15, 1959. 2 figs., 48 refs.

The value of determination of the serum glycoprotein level as a measure of rheumatic activity has been clearly demonstrated. In addition, various workers have attempted to define the fundamental modifications of the serum glycoproteins in the course of acute rheumatism and rheumatoid arthritis as an index of the evolutive stage of the disease. In acute rheumatism it has been found that an increase occurs in the glycoprotein level which is mainly due to an increase in carbohydrate bound to the α_2 -globulin fraction and is closely correlated with the activity of the disease process. In the active phase of rheumatoid arthritis changes in the serum glycoproteins are analogous to those found in rheumatic fever, but are quantitatively less marked. During the latent phase of rheumatoid arthritis the levels of protein-bound carbohydrates are normal. During the decline of activity of both diseases the serum glycoprotein levels diminish in the same degree, but may rise again when treatment is suspended.

These findings have been confirmed by the present authors, working at the Institute of Clinical Medicine and Therapeutics of the University of Pavia, in investigations on 22 patients aged 16 to 40, of whom 14 were suffering from acute articular rheumatism and 8 from rheumatoid arthritis in the active phase. A total of 33 blood specimens obtained from these patients by venepuncture at various stages were examined and compared with the findings in specimens from 30 healthy individuals aged 18 to 42. Diagnosis in the rheumatic cases was established on clinical grounds and confirmed by estimation of the erythrocyte sedimentation rate, antistreptolysin titre, and C-reactive protein level. It is concluded that estimation of the serum glycoprotein level, and in particular of the ratio of α_2 -globulin-bound carbohydrate to total α_2 globulin, constitutes the best method of estimating the degree of remission or persistence of the morbid process in rheumatic diseases.

Robert E. Lister

958. **Relation of Duration of Bed Rest in Acute Rheumatic Fever to Heart Disease Present 2 to 14 Years Later** B. L. LENDRUM, A. J. SIMON, and I. MACK. *Pediatrics* [Pediatrics] 24, 389-394, Sept., 1959. 4 refs.

An analysis is presented of the long-term results of the treatment of children with rheumatic fever without prolonged rest in bed. Of 360 patients followed up for more than 2 years after discharge from Herrick House, Bartlett, Illinois, 269 had been admitted immediately clinical evidence of acute rheumatic fever had dis-

appeared. As soon as temperature, sleeping pulse rate, leucocyte count, and erythrocyte sedimentation rate approached normal increasing activity was allowed. The average stay at the home was 3 months. The remaining 91 patients, who served as controls, had been admitted after prolonged periods of rest in bed. The cardiac status at the follow-up examination was assessed on the basis of significant changes in heart murmurs, change in size of the heart as seen radiologically, and changes in blood pressure indicating aortic incompetence. Assessment of the adequacy of medical care in both groups, including prophylaxis against streptococcal infection after discharge, showed that this care was slightly better in the control group.

Of the 269 patients in the experimental group, 169 were followed up for 2 to 4 years, 97 for 5 to 9 years, and 3 for 10 years or longer. In the control group 28 were followed up for 2 to 4 years, 57 for 5 to 9 years, and 6 for 10 years or longer. At the time of the final follow-up examination 62 (26%) of the experimental group were worse compared with 37 (41%) of the control group. When patients who had a recurrence (subacute bacterial endocarditis or "chronic myocarditis") were excluded 21 (12%) of the experimental group and 13 (25%) of the controls were worse. Of 100 patients in the experimental group followed up for more than 5 years, 16 were better, 51 were unchanged, and 33 were worse, whereas of the 63 controls, 9 (14%) were better, 25 (40%) were unchanged, and 29 (46%) were worse. Although the numbers are relatively small it is considered that they lend support to the view that prolonged rest in bed after an acute attack of rheumatic fever is "not necessary for optimal healing of the injured heart".

C. Bruce Perry

959. **The Treatment of Chorea with Corticosteroid Hormones.** (К вопросу о лечении хореи кортикостероидными гормонами) L. M. RYNSKAJA. *Клиническая Медицина* [Klin. Med. (Mosk.)] 37, 62-68, Sept., 1959. 26 refs.

The danger of valvular disease and heart failure resulting from chorea is particularly great in pregnant women; according to Wilson and Price the maternal mortality is 33% and the infant mortality 50%. The treatment of chorea with corticosteroids, which has been reported by various authors to have a rapid and beneficial effect, is therefore logical and justifiable.

In a series of 5 cases treated by the author "adreson" (cortisone), 50 mg. daily, was used in some cases and prednisone, 10 mg. daily, in others. Treatment lasted for at least 12 to 14 days and was combined with amidopyrine, salicylates, and sedatives. In all cases hyperkinesia ceased within a fortnight, but treatment was continued if signs or symptoms of active rheumatism remained. The only recurrence occurred in a pregnant woman of 22 with a 7-year history of chorea and mitral disease. She received cortisone, 50 mg. daily for 4 days,

followed by prednisone, 20 mg. daily for 10 days, by which time choreic movements had ceased. A week later there was a slight recurrence in the left hand, which disappeared in 4 days on resumption of treatment. She received in all 350 mg. of cortisone and 440 mg. of prednisone. Her pregnancy terminated with a normal live birth and there were no more relapses.

L. Firman-Edwards

CHRONIC RHEUMATISM

960. **The Serology of the Rheumatic Agglutination Factor.** (Zur Serologie des Rheumaagglutinationsfaktors) G. WIEDERMANN and F. REINHARDT. *Wiener Zeitschrift für innere Medizin und ihre Grenzgebiete* [Wien. Z. inn. Med.] 40, 303-305, Aug. [received Oct.], 1959. 11 refs.

An investigation was carried out at the Second Medical Clinic of the University of Vienna to determine whether the rheumatoid agglutination factor develops from globulins present in normal serum or whether it is based on a protein component not normally present. On the assumption that if the factor develops from normal serum globulins it should react with anti-human globulins such as Coombs serum a latex- γ -globulin system was saturated with rheumatoid factor and then incubated with Coombs serum. No significant fall in the titre of the Coombs serum, which would have indicated that a reaction with the rheumatoid factor had occurred, was found after incubation. It is therefore concluded that the rheumatoid factor is not derived from a component of normal human serum.

G. W. Csonka

961. **Results of Treatment with Hexadecadrol in Rheumatology.** (Résultats thérapeutiques de l'hexadécadrol en rhumatologie)

A. RUBENS-DUVAL, J. VILLIAUMEY, and D. LUBETZKI. *Semaine des hôpitaux de Paris* [Sem. Hôp. Paris] 35, 2441-2454, Sept., 1959. 7 refs.

The widespread use of adrenocortical steroids in the treatment of rheumatoid arthritis has led to much research into the production of derivatives of these substances which would retain their anti-inflammatory and anti-allergic properties while producing fewer or less serious side-effects. In this study the authors observed the effects of one of these derivatives, dexamethasone, in the treatment of 9 cases of rheumatoid arthritis, one of ankylosing spondylitis, 3 of lumbo-sciatica, and one of peri-arthritis of the shoulder. The patients were fully examined at the beginning and again after 4 to 6 weeks of treatment. The serum protein pattern was also determined electrophoretically and the erythrocyte sedimentation rate estimated.

The patient with ankylosing spondylitis received between 2.5 and 3.5 mg. daily for 9 weeks; although great relief was experienced, the side-effects, such as raised blood pressure, oedema, and capillary fragility, were severe. Of the 9 cases of rheumatoid arthritis, 8 responded dramatically, but the 9th patient, a man of 61 whose dosage reached 12 mg. daily, died suddenly; at necropsy the lungs showed grey hepatization and gastric ulceration was present. The activity of dexamethasone

appears to be 5 to 6 times that of prednisone, enabling relatively larger doses to be given, but the authors did not find that it was well tolerated, as has been suggested in the transatlantic literature. Insomnia, for example, was very troublesome in some of their cases. The remaining 4 patients obtained relief from pain such as would be expected from doses of 25 mg. of delta-cortisone (prednisone). Higher doses were tolerated because of the short duration of treatment. They conclude that while the therapeutic effect of dexamethasone is considerable, its administration entails a calculated risk.

D. Preiskel

962. **Intermittent Rheumatism. Palindromic Rheumatism, Intermittent Hydrarthrosis, and Allergic Rheumatism.** (Reumatismos intermitentes. Reumatismo palindrómico. Hidartritis intermitente. Reumatismo alérgico)

J. ROTÉS QUEROL and E. LIENCE. *Revista española de reumatismo y enfermedades osteoarticulares* [Rev. esp. Reum.] 8, 8-37, 1959. 47 refs.

The authors describe (from the Faculty of Medicine, Barcelona), the cases of 4 patients with palindromic rheumatism, 6 with intermittent hydrarthrosis, and 2 in which the condition corresponded to the description of "allergic rheumatism", these occurring among over 2,000 patients with various rheumatic diseases. Each of these three types of episodic arthritis is examined in detail and the relevant literature reviewed. In the 4 cases of palindromic rheumatism rapid, sometimes sudden, attacks occurred from 3 times a month to 3 times a year, and lasted at most 3 days, some being present for only a few hours. Usually only one joint was affected at a time, the proximal interphalangeal joints being most frequently involved, but any joint might be the site of an attack. Non-articular swelling was also seen in all 4 cases, this including a transient swelling of the palate which the authors considered might be "palindromic rheumatism of a mucosal cavity". One patient aged 84 had had the disease for 44 years without evidence of residual arthritis. The duration of the disease in the other 3 cases was 1, 2, and 9 years respectively.

In the 6 cases of intermittent hydrarthrosis attacks affected one or both knees (but usually one at a time) and occasionally other joints. Pain resulted from the distension by fluid and was relieved by aspiration of the joint. In one case the knees were involved alternately, causing considerable incapacity, while in another the arthritis followed a cyclic course, affecting the right knee, right hip, left knee, right ankle in that order with strict regularity. Some patients enjoyed longer periods of complete remission. The periodicity of the attacks varied from 9 to 18 days, but was constant for each patient. Three cases eventually showed evidence of rheumatoid arthritis and 2 of ankylosing spondylitis (representative case histories are given in detail). The 2 patients with "allergic rheumatism" had episodic pain or swelling of joints associated with angioneurotic oedema of the skin and other evidence of allergy.

The elaborate laboratory findings are tabulated and the differential diagnosis and treatment briefly discussed.

Allan St. J. Dixon

963. On the Elimination of Heterophile Agglutinins and Inhibitors in Serum Simultaneously with the Precipitation of the Rheumatoid Factor. Preliminary Report. [In English]

N. SVARTZ and K. SCHLOSSMANN. *Acta medica Scandinavica* [*Acta med. scand.*] **164**, 529-531, 1959. 6 refs.

The authors have previously shown that the haemagglutination test for rheumatoid arthritis can be improved by the separation of a moiety from whole serum by cold precipitation methods. This improvement consists mainly in increased specificity by the elimination of positive agglutination reactions due to pathological processes other than that of rheumatoid arthritis, and particularly systemic lupus erythematosus. In this paper from the King Gustaf V Research Institute, Stockholm, further improvements are reported, both in regard to results and in regard to the practicability of the procedure for routine use in clinical laboratories.

The new procedure consists in a modified method of fractionation of the serum with ammonium sulphate. To 1 ml. of inactivated serum is added 2 ml. of physiological saline and then, drop by drop, 1.3 ml. of saturated ammonium sulphate. This results in a final concentration of ammonium sulphate of 1.23 M. It is shown that the precipitate thus obtained contains almost all the rheumatoid factor. Furthermore, it is found that by this technique the substances having an inhibitory activity remain in the supernatant fluid, as also do the heterophile agglutinins. The technique thus obviates the necessity for absorption of the heterophile agglutinins in the standard sheep-cell test and eliminates the inhibitory substances of the reaction together with the agglutinins associated with other diseases. The question whether this technique further increases the specificity of this test as a diagnostic method for rheumatoid arthritis is to be considered in a later report. *Harry Coke*

964. Roentgen Manifestations of Senile Rheumatoid Arthritis. [In English]

P. SOILA and M. OKA. *Acta rheumatologica Scandinavica* [*Acta rheum. scand.*] **5**, 206-215, 1959. 11 figs., 11 refs.

At Kivelä Hospital, Helsinki, an analysis was made of the radiological appearances of the hands, feet, ankles, and knees of 115 patients (22 male and 93 female) aged 50 years and over in whom the duration of rheumatoid arthritis was 6 years or less. Severe changes, including deformities and ankyloses, were observed even within the first 18 months of the onset of the disease. Soft-tissue changes were easily discernible. Cystic changes were of little diagnostic value since they are common in a number of conditions, especially in this age group, but superficial eruptions of the cortex and expansions of cysts to the surface of the bone were reliable radiological manifestations of rheumatoid arthritis in this as in other age groups. Periosteal elevation and thickening were not seen. The authors state that rheumatoid arthritis in old age is not a quiescent process. They claim that in spite of the known unfavourable effects of age itself joint-space changes, deformities, carpal fusion, and ankyloses are less common in "senile" arthritis than in

rheumatoid arthritis in younger patients. [The validity of this would be easier to assess if the age distribution of the group and the method of case selection were given: "senile" is scarcely a valid description for the whole group.] *J. N. Agate*

COLLAGEN DISEASES

965. New Clinical Concept of Systemic Lupus Erythematosus

C. E. RUPE and S. N. NICKEL. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] **171**, 1055-1061, Oct. 24, 1959. 2 figs., 11 refs.

The natural history of systemic lupus erythematosus was studied at the Henry Ford Hospital, Detroit, in the medical records of 100 cases, in 83 of which a positive response had been obtained to the L.E.-cell test. From the analysis of the findings the authors consider that the disease runs a benign course (more than half of the patients survived at least 10 years) and is more common in males (34 in the series) than was previously thought to be the case, though it is less serious in males than in females. The occurrence of a streptococcal infection immediately before the onset is considered to be of aetiological significance. The prognosis was poor in patients with a butterfly rash or neurological manifestations, but appeared to be good in patients with a rheumatoid-like arthritis. *M. Wilkinson*

966. Psychoses Associated with Systemic Lupus Erythematosus

J. F. O'CONNOR. *Annals of Internal Medicine* [*Ann. intern. Med.*] **51**, 526-536, Sept., 1959. 2 figs., 21 refs.

The psychiatric manifestations of systemic lupus erythematosus were studied in 40 patients admitted to the Columbia-Presbyterian Medical Center, New York. During a follow-up period which averaged 3 years psychoneurotic symptoms developed in 5 of the patients and one or more psychotic episodes occurred in 21. The psychotic episodes were diagnosed as schizophrenic reactions in 9 cases, as depressive reactions in 3 cases, and as due to acute brain syndromes, with delirium or coma, in 11 cases. Only one of the 21 psychotic patients gave a history of previous psychiatric disorder and only 3 were not receiving steroids at the time of the episode, which often followed an increase in dosage. The author suggests that greater disease activity rather than higher steroid dosage correlated with the occurrence of psychotic episodes. Following remission of the disease and a reduction in the dosage of steroids the psychiatric manifestations invariably subsided, generally within one week. Subsequent restoration of the full dosage of the steroid did not usually cause exacerbation of the psychosis, and the author therefore recommends that steroid therapy need not be withdrawn because of psychiatric symptoms if its use is indicated for other aspects of the disease.

Of 11 cases which came to necropsy, 10 showed evidence of brain damage secondary to endarteritis, and in all of these psychiatric or neurological syndromes had been present during life. *M. Wilkinson*

Neurology and Neurosurgery

967. Sweat Patterns and Skin Temperatures in Patients with Brain and Spinal Cord Lesions

G. M. ROTH, H. D. TRELLE, J. G. RUSHTON, and E. C. ELKINS. *Journal of the American Medical Association [J. Amer. med. Ass.]* 171, 381-385, Sept. 26, 1959. 4 figs., 3 refs.

At the Mayo Clinic the skin temperature of the fingers and toes and the sweating response to heating of the whole body were studied in 30 patients suffering from neurological disease or injury. In 5 out of 6 patients with residual paralysis from anterior poliomyelitis the responses were normal; in the sixth, a woman who had had poliomyelitis 36 years previously, sweating was confined to the front of the arms and back of the legs. Of 6 patients with brain disease, very slight abnormalities were found in 2. There were 10 patients with compression of the spinal cord below C.8 segment, and in 9 there were sweating abnormalities which could be correlated with the level of the lesion and subsequent surgical procedures. All but one of 8 patients with compression of the cord at or above C.8 segment had complete anhidrosis of the body, and in the remaining one sweating occurred only over the left side of the head and neck and left arm. In some patients with injuries of the spinal cord vasoconstrictor fibres were damaged, but not sweating fibres, which seems to indicate a difference in the distribution of these fibres within the spinal cord.

J. W. Aldren Turner

969. Electroencephalographic Studies in Respiratory Failure

L. A. G. DAVIDSON and J. M. JEFFERSON. *British Medical Journal [Brit. med. J.]* 2, 396-400, Sept. 12, 1959. 3 figs., 16 refs.

The authors studied the changes in the electroencephalogram (EEG) in 16 patients, aged 46 to 73, admitted to Queen Elizabeth Hospital, Birmingham, with acute or subacute pulmonary insufficiency with carbon dioxide retention and with or without congestive heart failure. Arterial blood gas values and the EEG recordings were studied on the same day, in most cases simultaneously.

The EEG showed symmetrical changes from intermittent theta activity to paroxysmal delta discharges of high amplitude, the changes resembling those seen in other confusional states, especially those of metabolic origin. A definite relationship was observed between the abnormality in the EEG and the clinical neurological findings. There was also some association between the EEG abnormality and the degree of hypoxia and hypercarbia, although the connexion was not clear in individual cases. No other relationships were noted.

Attention is drawn to the wide range of individual differences in cerebral homeostasis and central nervous system tolerance of alterations in blood gas levels, the blood gas values not being clearly related to neural and mental signs and symptoms.

J. L. Standen

968. Effect of "Ciba 13.155" in the Treatment of Spastic Paraplegia. [In English]

E. PEDERSEN and P. SCHLEISNER. *Acta psychiatrica et neurologica Scandinavica [Acta psychiat. scand.]* 34, 342-353, 1959. 1 fig., 5 refs.

Ciba 13.155 is a polysynaptic inhibitor of the central nervous system, its chemical formula being 2-hydrazino-4:6-bis-diethylamino-1:3:5-triazine dihydrochloride. At Aarhus Kommunehospital (University of Aarhus), Denmark, the drug was used in the treatment of 50 patients with various spastic disorders such as disseminated sclerosis, hemiplegia, and subacute combined degeneration of the spinal cord. At first it was given in doses of 50 mg. 3 times a day by mouth. Subsequently the optimum dosage was found to be in the region of 6 mg. per kg. body weight per day. The gait improved in 29 of the cases, but the most surprising and unexpected result was the improvement in bladder control of 12 patients with frequency and incontinence. The most frequent side-effects were mild heartburn and epigastric pain, which could probably be avoided by coating the tablets of the strongly acid drug. It would seem that this substance may prove to be the most useful so far produced for the relaxation of muscular tone in spastic disorders.

G. S. Crockett

BRAIN AND MENINGES

970. Neurophysiological Observations on the Mechanism of Attention in Man. (Documents neurophysiologiques relatifs aux mécanismes de l'attention chez l'homme)

M. JOUVET, B. SCHOTT, J. COURJON, and G. ALLÈGRE. *Revue neurologique [Rev. neurol.]* 100, 437-450, May [received Sept.], 1959. 11 figs., 22 refs.

This neurophysiological investigation of the mechanism of attention in man was carried out at the Neuropsychiatric Clinic, Faculty of Medicine of Lyons, on 8 patients by means of electroencephalography (EEG) with subcortical, concentric, bipolar electrodes inserted into the right occipital lobe at the level of the optic radiations. Light stimulation of high intensity was produced by an electronic apparatus situated at 50 cm. from the subject's head, and the flashes were recorded on the EEG by means of a photoelectric cell fixed on the eyelids, the eyes being closed during the recordings. In 5 of the 8 cases the recordings were made while the patient was undergoing air ventriculography in an attempt to locate a tumour which had not given a convincing angiographic picture and in the other 3 cases to investigate a syndrome of intracranial hypertension.

The visual subcortical responses recorded on the EEG were obtained in total silence after the subject had become accustomed to the conditions.

The responses appeared in the EEG as a diphasic rapid wave initially positive, followed by a slow diphasic wave initially negative. The maximum frequency of the intermittent light stimulation varied from 20 to 30 flashes per second, according to the subject. There was some fluctuation in the amplitude of the responses which was difficult to relate to subjective factors, although it was noted that the slightest noise caused a decrease in amplitude. Visual attention, obtained by asking the subject to count the flashes at about one per second, produced rapid low-voltage activity on the scalp in the occipital region and augmentation of the amplitude of subcortical potentials. However, when the visual responses were recorded while the subject's attention was directed to other sensory modalities there was a reduction in amplitude, sometimes almost to the point of disappearance. This blockage was seen particularly on painful stimulation, such as pricking the thigh. Olfactory stimulation also produced "blockage", and auditory stimulation produced a diminution of amplitude. Tactile recognition of objects placed in the subject's hand produced the least important degrees of blockage.

Further records were made on 2 patients (during the operation of thalamic coagulation for intractable pain) by means of electrodes placed in the ventro-postero-lateral nucleus of the thalamus, and it was found that attention to other stimuli partly blocked the response to a tactile rhythmic stimulus applied to the skin of the face.

The authors conclude that attention is one of the essentials of the perceptivity of a signal. They were unable to determine at what level the "blockage" occurs, but suggest that the reticular formation plays an important part, supporting this view by describing a case without blockage in which there was an undoubted mesencephalic lesion. They agree on the other hand that the central mechanisms causing blockage could emanate from the cortex.

J. MacD. Holmes

971. The Intravenous Use of Urea for Control of Intracranial Hypertension

J. S. MARSH and F. M. ANDERSON. *Bulletin of the Los Angeles Neurological Society* [Bull. Los Angeles Neurol. Soc.] 24, 174-179, Sept., 1959. 7 refs.

In 1958 Javid (*Surg. Clin. N. Amer.*, 38, 907) described a trial of intravenous administration of a 30% solution of urea for the reduction of raised intracranial pressure in a total of 300 cases. The present authors used this solution in 43 patients at Los Angeles County Hospital who were judged to have cerebral oedema, a total of 113 doses of 0.5 to 1.5 g. of urea per kg. body weight being administered. Of 58 separate doses given in the post-operative period, 31 were followed by improvement, while 26 did not have any noticeable effect; in one instance the patient died from irreversible hypotension. No correlation was observed between the dose of urea and the clinical response. There was no rebound of

intracranial pressure to an excessively high level as occurs after administration of hypertonic glucose. Side-effects of intravenous injection of urea were subcutaneous necrosis and venous thrombosis.

The authors consider that the use of this 30% solution of urea is justified in patients with cerebral oedema; the substance is not infallible, but it can be given with ease, is well tolerated by patients with satisfactory renal function, and in the vast majority does not cause any untoward reactions.

J. V. Crawford

972. Six Cases of Cerebellar Atrophy of the Late Cortical Type (Marie-Foix-Alajouanine) in Chronic Alcoholics. (Sur six cas d'atrophie cerebelleuse du type cortical tardif (Pierre-Marie-Foix-Alajouanine) observés chez des alcooliques chroniques)

T. ALAJOUANINE, P. CASTAIGNE, F. CONTAMIN, and J. LEBOURGES. *Revue neurologique* [Rev. neurol.] 100, 411-429, May [received Sept.], 1959. 2 figs., 42 refs.

The authors describe 6 cases of cerebellar atrophy, all of very similar symptomatology, which they consider to be cases of cerebellar cortical atrophy, although anatomical verification was not possible. Signs of cerebellar involvement were most evident in the lower limbs, there being difficulty in standing and walking which was of slowly progressive evolution. In 5 of the cases air encephalography showed an isolated but clear-cut dilatation of the cisterns of the posterior fossa, in particular the supracerebellar cistern in its anterior part, sometimes with widening of the cortical sulci.

The authors discuss the numerous classifications of the cerebellar atrophies and conclude from the symptomatology, slow evolution, and the radiological location of a lesion in the antero-superior part of the cerebellum in their cases that they resemble or are identical with the cases of cerebellar cortical atrophy first described by Marie, Foix, and Alajouanine (*Rev. neurol.*, 1922, 38, 850 and 1082), except that in the present cases alcoholic intoxication of long duration was a prominent factor, while undoubtedly complex nutritional and metabolic disturbances associated with the chronic alcoholism were also present. They point out that although chronic alcoholism is far from rare, cerebellar atrophy is a rare complication and they suggest that some additional constitutional "fragility" of the nervous system must play a part in the aetiology of this type of cerebellar atrophy.

J. MacD. Holmes

973. The Functions of the Reticular Formation of the Brain-stem, and Certain Clinical Problems. (Функции сетевидного образования ствола головного мозга и некоторые вопросы клиники)

S. P. NARIKAŠVILI. *Клиническая Медицина* [Klin. Med. (Mosk.)] 37, 20-27, Sept., 1959. 6 figs., bibliography.

This article gives a detailed account of the structure of the reticular formation, of the ascending and descending tracts which traverse it or send collateral fibres to it, and of the effects resulting from stimulating or depressing its function. Stimulation of the medial fibres causes inhibition of reflexes and of motor movement in the

trunk and limbs, while stimulation of the lateral fibres facilitates them. In the same way movements due to stimulation of the cerebral cortex are inhibited or facilitated. One of the functions of the reticular formation, therefore, is to regulate the response of the spinal centres to cerebral control. In addition stimulation of the reticular formation causes arousal from sleep, with corresponding changes in the electroencephalogram, the slow waves of high amplitude being replaced by more rapid waves of low amplitude.

The author demonstrates the fact that the cerebrum receives stimuli from the spinal sensory tracts by two channels—one direct and the other via the reticular formation. Damage to the formation causes prolonged and deep sleep in the experimental animal, but if the "classic" nerve-paths to the cerebrum are damaged without involving the reticular path this does not occur. The author suggests that one of the functions of the reticular formation is to maintain the sensitivity of the cortex to sensory stimuli. At the same time there is clear evidence that the formation can be stimulated to activity not only from below (by afferent stimuli), but also from above, from the cortex—that is, the effect is reciprocal. Thus the cortex can be shielded from afferent stimuli up to a certain level, and this shielding can be selectively controlled to some extent by cortical action on the reticular formation. These hypotheses, however, are based on experimental observations in animals, and so far no direct knowledge has been obtained as to what happens in man under normal living conditions. Many problems still await further investigation.

(The bibliography contains 13 Soviet and 65 foreign references.)

L. Firman-Edwards

974. **On So-called Malignant Exophthalmos.** (О так называемом злокачественном экзофтальме)
D. R. ŠTUL'MAN. *Клиническая Медицина [Klin. Med. (Mosk.)]* 37, 76-85, Sept., 1959. 1 fig., 19 refs.

This article is based on the detailed investigation of 52 patients suffering from malignant exophthalmos, which was demonstrated by Dobyns and Steelman (*Endocrinology*, 1953, 52, 705; *Abstr. Wld Med.*, 1954, 15, 57) to be caused by a secretion of the pituitary gland distinct from the thyroid stimulating hormone. Of the 52 patients, 20 had undergone thyroidectomy before investigation. At the time of examination 32 were euthyroid, 17 thyrotoxic, and 3 hypothyroid. In only 5 cases was the exophthalmos completely unilateral, though the degree of proptosis was usually unequal. Keratitis was present in 11 of the patients; intra-ocular pressure was increased in 13. Ophthalmoplegia was present to some extent in all cases, but in only 3 was it total. Transient or permanent diplopia was present in 26 cases. Paralysis of the intrinsic muscles was rare, and it appears probable that the external ophthalmoplegia is due to muscular changes and not to a lesion of the mesencephalon.

Abnormalities of the olfactory nerves were present in 4 cases and of the facial and lingual nerves in 20; the knee-jerks were unequal in 22 cases, the abdominal and plantar reflexes abnormal in 13, and the ankle and wrist

reflexes abnormal in 11. Signs of a "pseudo-bulbar" complex, such as increased jaw-jerk, were found in 15 cases, sensory changes in 4, and incoordination in 9. Two cases were of special interest in relation to the possible cerebral pathogenesis of this disease; in one the exophthalmos arose on a background of severe post-encephalitic parkinsonism, while in the other it was one of the manifestations of a diffuse gliomatosis of the central nervous system. Electroencephalograms were recorded in 35 cases and in about one-third of them revealed evidence of disturbances of conduction in the tracts of the brain-stem. Symptoms of a diencephalic syndrome were also observed in the form of increased appetite in 22 cases, polydipsia in 27, pathological blood sugar curve in 23, and increased blood cholesterol content in 15 (of 32 cases). Liver tests in these cases excluded hepatic dysfunction. In 19 patients craniography showed changes indicative of cranial hypertension. Headache was a serious complaint in 28 cases, and 25% of the patients gave a history of vomiting compared with 4% in a series of cases of thyrotoxicosis reported by Khavin. Temperature control was defective in 10 patients.

The treatment of choice is irradiation of the diencephalon, together with injections of ACTH (corticotrophin) up to a total of 600 to 800 units and cortisone drops for the eyes. Dark glasses, limited fluid intake, dehydration therapy, vitamins A, B, and C, and sulphacetamide ointment in a soft paraffin base for application to the corneal surfaces are recommended. The disease is subject to remissions, but cure is rare. Thyroidectomy should be avoided in cases of thyrotoxicosis with pronounced exophthalmos.

L. Firman-Edwards

975. **The Clinical Signs and Morphology of Tumours of the Corpora Quadrigemina.** (К клинике и морфологии опухолей четверохолмия)

M. G. FAJNBERG. *Журнал Невропатологии и Психиатрии [Z. Neuropat. Psihiat.]* 59, 1042-1048, No. 9, 1959. 3 figs., 8 refs.

This paper is based on a study of 24 cases of tumour of the corpora quadrigemina occurring in 15 male and 9 female patients, 3 of whom were under the age of 10, 5 were aged from 11 to 20, 4 from 21 to 30, 3 from 31 to 40, and 9 were over 40. Of the 23 primary tumours, 13 (10 of them astrocytomata) were in the corpora, 8 in the pineal gland, and 2 in the membranes covering the corpora quadrigemina; the remaining tumour was a metastasis from a prostatic carcinoma. Of the first group, apart from the astrocytomata, the other three were a multiform spongioblastoma, a congenital cyst with oligodendrocytoma, and an angioreticuloma. The 8 pineal tumours included 3 pineocytomata and one case each of pineocytoblastoma, neuropithelioma, ependymoblastoma, undifferentiated astrocytoma, and teratoma. Of the 2 tumours of the membrane, one was a fibroblastoma and one an arachnoid endothelioma. The author divides these tumours into three groups: (1) those involving the anterior and posterior corpora and the central grey matter around the Sylvian aqueduct and the oculomotor nuclei; (2) those involving the roof

of the midbrain, the upper part of the red nucleus, and the anterior cerebral peduncles; and (3) those involving, in addition to the above, the substantia nigra and crista on one or both sides.

The clinical features produced by these tumours are headache, nausea and vomiting, somnolence, thirst, increase of appetite, and psychological disturbances such as euphoria, complacency, addiction to trivial jokes, untidiness, and in some cases loss of memory, disorientation in space and time, and confabulation. Oculomotor disturbances (more especially of pupillary reactions and upward movement) and abnormal muscular tonus were found to be the earliest localizing signs. In 13 cases of tumour of Group 2, which is by far the commonest, decerebrate rigidity was present in 5. In the 3 cases of Group 3, the rarest type, hemiparesis was present in all 3. In contrast to cerebellar tumours, incoordination was rare. Muscular tonus was reduced in 7 cases, increased in 9, and in 5 cases alternated between hypotonus and plastic hypertonus, while 9 patients showed adiposogenital dystrophy and loss of thermal regulation. Internal hydrocephalus of the third and lateral ventricles is a common feature in the later stages, and opisthotonos and other contractures are of very frequent occurrence. Craniography often reveals changes in configuration of the sella turcica and evidence of hydrocephalus, with thinning of the cranial bones. L. Firman-Edwards

976. **Difficulties and Mistakes in Diagnosis of Tumours of the Corpus Callosum.** (Затруднения и ошибки в диагностике опухолей мозолистого тела)
K. V. ŠIMANSKIJ. *Журнал Невропатологии и Психиатрии* [Ž. Nevropat. Psihiat.] 59, 1057-1061, No. 9, 1959. 7 refs.

The author has investigated 11 cases of primary tumour of the corpus callosum—seen among a total of 224 confirmed cases of intracranial neoplasm—of which 6 arose in the splenium and 5 in the anterior portion, that is, in the genu or rostrum. The tumours were of various types, and included multiform spongioblastomata, astrocytomata, polar spongioblastomata, angiotreticuloma, and one glioma of undetermined character. In only 4 cases was the correct diagnosis established before operation, in many of the others a vascular or inflammatory lesion being suspected. There was thus a much higher percentage of error in respect of tumours at this site than in intracranial tumours situated elsewhere, one of the reasons for this being the mildness or absence of symptoms of intracranial pressure in the early stages, as has been noted by other workers.

Both headache and signs of congestion in the optic fundi were minimal or absent in nearly half the patients, while in 6 out of 10 patients the cerebrospinal fluid showed pleocytosis, such a proportion being exceeded only in cases of diffuse carcinomatosis of the pia-arachnoid membranes. The author states that in these cases apraxia, epileptiform seizures, and involvement of the cranial nerves are rare; the most suggestive symptoms are loss of memory and disorientation in space and time in patients with tumour of the splenium, and disturbances of personality and absence of activity in those with

tumour in the anterior part of the corpus callosum. He emphasizes the frequency of symptoms of "derealization" and sensory aphasia in patients with splenial tumour, the mental picture resembling that of Korsakov's syndrome, except that there is no confabulation.

L. Firman-Edwards

977. **Clinical and Radiological Diagnosis of Tumours of the Lateral Cerebral Ventricles.** (К клинико-рентгенологической диагностике опухолей боковых желудочков головного мозга)
E. M. GOL'CMAN. *Журнал Невропатологии и Психиатрии* [Ž. Nevropat. Psihiat.] 59, 1082-1087, No. 9, 1959. 44 refs.

Primary tumours arising in and confined to the cavities of the lateral ventricles are among the rarest forms of brain tumour. The commonest histological types are ependymoma and papilloma of the choroid plexus, but oligodendrioma and astrocytoma also occur. Less common is a meningioma (nearly always located in the posterior horn) and rarer still angiotreticuloma. The clinical diagnosis is difficult owing to the lack of distinctive locating signs. Pneumoventriculography is the most reliable diagnostic method. Cushing described five basic symptoms or signs suggestive of these tumours: (1) headache on the side of the tumour; (2) contralateral hemianopia; (3) contralateral hemiparesis and hemianaesthesia; (4) pseudocerebellar symptoms; and (5) in lesions of the left lateral ventricle, alexia and other related disorders.

The present paper is based on the author's experience of 27 cases occurring in patients aged from 16 months to 55 years. The history of the illness varied from 1 month to 8 years. All the patients had headache of paroxysmal type, which was of increasing severity in most cases (but in 5 was severe from the beginning); in 21 cases this was accompanied by vomiting. Other signs and symptoms were general weakness, defect or loss of memory, somnolence, disorientation, deafness, and inhibition. Hemiparesis occurred in 9 patients, 3 of whom also had hemianaesthesia; central facial nerve paralysis was common, but paresis of the 3rd, 6th and 12th nerves was present in only one case each. Motor aphasia was observed in 3 patients and optical hallucinations in 4. Calcification was seen in 5 out of 25 craniograms, and the ventriculographic appearances were typical in 16 cases.

L. Firman-Edwards

978. **Clinical and Electroencephalographic Considerations in the Diagnosis of Carotid Artery Occlusion**
W. K. HASS and E. S. GOLDENSOHN. *Neurology* [Neurology (Minneapolis)] 9, 575-589, Sept., 1959. 10 figs., 25 refs.

The authors have reviewed the clinical and electroencephalographic (EEG) findings in 35 patients who were treated at the Neurological Institute, Presbyterian Hospital, New York, between 1949 and 1957 and in whom the diagnosis of carotid occlusive disease was confirmed by arteriography (31 cases), post-mortem examination (2 cases), angiocardiology (1 case), or operation (1 case). There were 26 men and 9 women, and their

ages ranged from 40 to 73 years, the average being 56. The left internal carotid artery was involved in 20 patients, the right in 11; the occlusion was complete in 27 cases and partial in 4. Episodic ischaemic attacks were the presenting symptom in 22 cases, the contralateral weakness was slowly progressive in 1, and the onset was sudden and persistent in 3. The symptoms included weakness or paraesthesiae in one arm (18 cases) or in the face, aphasia (8 cases), hemiparesis progressing to hemiplegia (4 cases), numbness in the leg (2 cases), and mental disturbance (3 cases).

Arteriography was performed on 32 patients, but was unsuccessful in one; unilateral studies were made in 27 cases, bilateral in 4. One patient developed generalized convulsions and 4 increasing contralateral weakness after unilateral arteriography; there were no untoward effects in the 4 patients who had bilateral injections. Four of 6 patients who underwent air encephalography showed marked deterioration following the procedure. The EEG was normal at a time when symptoms were present in 8 cases, but subsequently became abnormal in 3 of these. In the remaining cases the EEG was abnormal throughout. The abnormalities usually took the form of focal slow-wave activity over the affected hemisphere, but sometimes focal depression in voltage of normal activity was the only abnormality. The incidence of abnormalities (83%) was similar to that observed in cases of brain tumour. The severity of the EEG abnormality usually ran parallel to the extent of clinical abnormality; in many cases the EEG remained abnormal for several months and sometimes for as much as one year.

John N. Walton

979. Surgical Treatment of Lesions Producing Arterial Insufficiency of the Internal Carotid, Common Carotid, Vertebral, Innominate and Subclavian Arteries

M. E. DE BAKEY, E. S. CRAWFORD, and W. S. FIELDS. *Annals of Internal Medicine* [Ann. intern. Med.] 51, 436-448, Sept., 1959. 4 figs., 17 refs.

In this paper from Baylor University College of Medicine, Houston, Texas, the authors discuss a series of 305 cases of cerebral arterial insufficiency, in 122 of which arteriography revealed the presence of extracranial arterial occlusion. The causative factor in most of the cases was atherosclerosis. Although multiple lesions were common (43% of cases), the disease pattern showed two forms—a proximal and a distal form. In the proximal form the stenosing lesions were situated in the innominate, left common carotid, and left subclavian arteries near their origin from the aortic arch; in most cases the vessels distal to the lesion were patent. In the distal form the lesions were in the internal carotid or vertebral arteries close to their origin.

The symptoms and signs in patients with the proximal form were referable to both the cerebrum and the upper limbs. Pulse and blood pressure might be diminished or absent in an upper limb and sometimes ischaemic cutaneous lesions were seen in the hands. A systolic bruit was frequently heard at the base of the neck. Symptoms and signs in the distal form were mainly cerebral, and recurrent attacks of hemiparesis and aphasia were

common. A systolic bruit was sometimes heard at the angle of the jaw and contralateral carotid compression could cause syncope. The incidence of hypertension and of heart disease in these patients was high.

Of the 122 patients, 106 (85 male and 27 female, aged 24 to 71 years) were considered suitable for surgical treatment, which consisted in endarterectomy or graft by-pass, the latter procedure being used in cases of proximal lesions. Pulsatile circulation was restored in all cases with proximal lesions, in 97% of those with lesions of the internal carotid artery, and in 66% of those with vertebral lesions. In the 106 patients there were 174 lesions and 149 of these were explored surgically; of these, 136 were considered to be operable and a pulsatile circulation restored in 133. All patients with lesions of the great vessels were completely relieved of symptoms and the majority of those with lesions of the internal carotid and vertebral vessels were either relieved or improved. The authors state that these patients have been followed up for periods of over 5 years and the improvement has been well maintained.

Brodie Hughes

980. Serum Lipid and Cholesterol Levels in Cerebrovascular Disease

J. S. MEYER, A. G. WALTZ, J. W. HESS, and B. ZAK. *A.M.A. Archives of Neurology* [A.M.A. Arch. Neurol.] 1, 303-311, Sept., 1959. 32 refs.

This paper from Wayne State University College of Medicine, Detroit, reports a statistical analysis of the results of estimations of the serum cholesterol and lipid levels in 110 patients with cerebrovascular disease (mean age 55.5 years). No significant difference was found between these patients and a group of 79 patients of comparable age (mean 51.8 years) with non-vascular disease. However, comparison with a group of 22 young healthy men (mean age 30 years) revealed a tendency for both values to increase with age.

N. S. Alcock

981. Rheographic Findings during Headache. I. Experimental Histamine Headache and Certain Non-paroxysmal Clinical Types of Headache (Febrile, Inflammatory, and Hypertensive Headache). (Indagini reografiche in corso di cefalea. Nota I. La cefalea sperimentale da istamina ed alcune cefalee cliniche non parossistiche (cefalea febbrile, cefalee flogistiche, cefalea degli ipertesi))

V. BARTOLI, P. ARCANGELI, M. MILANO, and A. ARCANGELI. *Rivista critica di clinica medica* [Riv. crit. Clin. med.] 59, 25-45, Feb. [received Sept.], 1959. 14 figs., 16 refs.

Working at the University of Florence, the authors have employed an electromanometric method [details of which are not given], which in effect records the endocranial pulse waves on either side simultaneously, in the investigation of various types of headache. The method is painless and can therefore be used for the study of cerebral vasomotor changes in patients without disturbing them. After the intravascular injection of histamine serial recording of the pulse waves shows that the onset and duration of the headache is independent of any changes in the character of the pulse waves. They

therefore consider that the purely vascular hypothesis of the causation of headache in these circumstances must be discarded in favour of a more complex mechanism in which hypothetical pain-producing substances are released in response to tissue changes. In febrile headache they find a similar lack of relation between the headache and pulse changes, and they conclude that the important factor here is a lowering of the threshold of sensitivity as a direct result of the febrile state, together with vasodilatation. Again in serous meningitis and in chronic basal meningitis they conclude from their observations that vasomotor factors are secondary to, and not primarily responsible for, the headache. In essential hypertension they report the same lack of correlation between the changes in the pulse waves and the occurrence of headache.

In a careful discussion of these observations the authors find themselves unable to subscribe to the usual vascular hypothesis of the causation of headache. They consider that it is necessary to invoke tissue factors and particularly the release of pain-producing substances. The role of increased sensitivity due to general factors is also stressed.

J. B. Cavanagh

982. Rheographic Findings during Headache. II. Migraine and the Pseudomigraine Syndrome. (Indagini reografiche in corso di cefalea. Nota II. L'emigrania e le sindromi pseudoemigraniche)

P. ARCANGELI, M. MILANO, and A. ARCANGELI. *Rivista critica di clinica medica* [Riv. crit. Clin. med.] 59, 46-71, Feb. [received Sept.], 1959. 7 figs., 32 refs.

Using an electromanometric method of recording the pulse waves inside and outside the skull [see Abstract 981] the authors have carefully studied 7 patients with migraine and 9 with pseudomigrainous attacks. During the first (prodromal) phase of migraine frequent irregularities occur in the amplitude and form of the pulse waves. In the second phase, when scotomata are perceived, there are marked variations in the amplitude of the pulse on the side subsequently showing headache. During the third (headache) phase, there is an increase in the amplitude of the pulse waves varying from 25 to 100% and the waves are very polymorphic. These changes continue into the recovery phase, when the waves steadily return to normal.

The authors analyse these findings in relation to the march of the migrainous process. They conclude that in migraine there are indications that the vasomotor disturbances originate in the central regulating mechanism of autonomic function rather than in a constitutional disturbance of the vasomotor system alone. These disturbances are critically accentuated on the approach of an episode, but the authors believe that the vasomotor disturbance is not primarily responsible for the train of symptoms. They find that the visual disturbances and the headache are of obscure origin, and they certainly cannot demonstrate any vasospastic background to them. Moreover, they are unable to correlate the onset of headache with any specific changes in the character of the pulse waves. They believe that tissue factors and the release of pain-producing substances are again neces-

sary parts of the mechanism of production of the symptoms. Variations in sensitivity and refractoriness to these factors may account for the varying frequency of the migrainous episodes, but they believe the real centre of initiation to be in the diencephalon.

In contrast to migraine, pseudomigraine associated with chronic focal meningitis is accompanied by a reduction in amplitude of the cranial pulse waves. The authors consider this to be the result of oedema in the chronically inflamed area. Pseudomigraine with a "trigger" area in the neck muscles on the other hand is accompanied by a rise in amplitude of the pulse waves. This is rapidly reduced to normal by analgesic drugs and is considered to be a response to the pain.

J. B. Cavanagh

EPILEPSY

983. A Correlation of Clinical, Electroencephalographic and Anatomical Findings in Nine Autopsied Cases of "Temporal Lobe Epilepsy". [In English]

H. GASTAUT, M. TOGA, J. ROGER, and W. C. GIBSON. *Epilepsia* [Epilepsia (Amst.)] 1, 56-85, March [received Oct.], 1959. 19 figs., 6 refs.

The authors of this paper from the University of Marseilles give an account of the clinical, electroencephalographic, and pathological findings in 9 cases of temporal-lobe epilepsy and discuss the correlations between these findings. The lesions found at necropsy included parasitic cysts, cholesteatoma, and intracerebral haematoma in addition to atrophic lesions.

In discussing the aetiology of these atrophic cases the authors recall the hypothesis of compression of the anterior choroidal and posterior cerebral arteries against the edge of the tentorium during prolonged labour, producing sclerosis of the temporal lobes leading to seizures in later life. They then discuss the probability of a similar vascular compression being responsible for some of the cases of acquired epilepsy in adult life. They postulate an initial vascular lesion (usually a venous thrombosis) which precipitates cerebral oedema which in turn causes herniation of the uncus on one or both sides with compression of the anterior choroidal and posterior cerebral arteries. This compression may lead to ischaemic lesions in the cortical areas supplied by these vessels (uncus, parahippocampal gyrus, and Ammon's horn). They also discuss the importance of anatomical lesions which have long been described in chronic epileptics in the region of Ammon's horn and give their reasons for believing that these lesions are the cause of the seizures and not the result of them.

J. B. Stanton

984. Subcortical Recording in Temporal Lobe Epilepsy. R. S. LICHTENSTEIN, C. MARSHALL, and E. A. WALKER. *A.M.A. Archives of Neurology* [A.M.A. Arch. Neurol.] 1, 288-302, Sept., 1959. 10 figs., 5 refs.

From Johns Hopkins University School of Medicine, Baltimore, is reported a study of 14 patients who had medically uncontrollable psychomotor epilepsy and were being considered for temporal lobectomy. However,

because some of the seizures or the electroencephalograms were atypical it was decided to confirm that the epileptic discharges were actually coming from the temporal lobe, and subcortical areas were therefore investigated by means of depth electrodes. Perforations were made in the frontal, parietal, and temporal regions and 6 electrodes of 38-gauge double "formvar" nichrome wire were inserted at each site, the bared tips of the 6 strands of wire being staggered at 1-cm. intervals. Every effort was made by pneumoencephalography and other means to locate the tip of each wire accurately. Usually the wires were left in place for 10 to 30 days, recordings being made at intervals of one to 3 days. In addition to ordinary recordings made in the usual way and also with activation techniques, electrical stimulation of the depth electrodes was carried out.

Details of the findings in 2 representative cases are given and some of the results of stimulation in various regions described. Of the 14 patients, 7 showed typical seizures and temporal spike foci, 5 typical seizures but diffusely abnormal surface recordings, and 2 had bizarre seizures. The authors conclude that with this method of investigation a better choice of patients likely to benefit from temporal lobectomy can be made.

N. S. Alcock

985. Ethchlorvynol in the Treatment of Mixed Grand and Petit Mal Epilepsy. [In English]
C. H. CARTER. *Epilepsia* [*Epilepsia* (Amst.)] 1, 110-114, March [received Oct.], 1959. 2 refs.

This article from the Sunland Training Center, Gainesville, Florida, describes the results obtained in the treatment of epilepsy with a new anticonvulsant, ethchlorvynol ("placidyl"), which is 1-chloro-3-ethyl-1-penten-4-yn-3-ol. The 49 patients treated were mostly children suffering from mixed grand mal and petit mal whose attacks had been controlled so far as possible with other anticonvulsants. The year before treatment with ethchlorvynol was started was used as a control period. In some cases ethchlorvynol was used alone, but in most it was given in association with the drug previously used, the dosage generally being 100 mg. 3 times a day. The maximum dosage used was 300 mg. 3 times a day. The average length of the test period was 4-25 months, and the effects of the new drug on grand mal and petit mal seizures were evaluated separately.

Complete control of both types of epilepsy was obtained in 6 patients, and of grand mal alone and petit mal alone in 6 patients in each case. Partial control of one or both types of fit was obtained in 18 patients, and in 13 patients the treatment was regarded as a failure, the frequency of both types of fit being considerably increased. The increase in the number of seizures in these 13 cases was on average greater than the average decrease in patients who were benefited. No evidence of toxicity of the drug was detected by routine blood counts, urine tests, and liver function tests.

The author concludes that ethchlorvynol has a place in the management of severe and refractory cases of mixed grand mal and petit mal epilepsy, but that in about 25% of cases it may cause an increase in seizure frequency.

J. B. Stanton

SPINAL CORD

986. Failure of Amyotrophic Lateral Sclerosis to Respond to Intrathecal Steroid and Vitamin B₁₂ Therapy
S. J. L. PIEPER and W. S. FIELDS. *Neurology* [*Neurology* (Minneapolis)] 9, 522-526, Aug., 1959. 7 refs.

This paper from Baylor University College of Medicine, Houston, Texas, records the results of the experimental treatment of 26 patients suffering from amyotrophic lateral sclerosis, all of whom were natives of Guam, where the disease is exceptionally common. This consisted in the intrathecal injection of vitamin B₁₂ (cyanocobalamin) in doses of 1,000 mg. [this dosage is repeatedly given as milligrammes, not microgrammes as might be expected] together with hydrocortisone sodium succinate, 50 mg. in 2 ml. of water. The injections were given either once a week on an out-patient basis or in courses of 4 daily injections once a month to in-patients, who received 16 or more such injections; 18 became more severely affected or died, while 2 patients remained unchanged and one improved slightly for a short time. One of the remaining 5 died of an intercurrent infection and the others refused further treatment after a few injections. The treatment thus completely failed to influence the disease. There were no clinical complications of the intrathecal injections, but in 4 cases necropsy showed gross adhesions of the spinal dura to the vertebral column at the site of injection.

J. MacD. Holmes

987. Familial Amyotrophic Lateral Sclerosis. (La sclérose latérale amyotrophique familiale)
M. BONDUELLE, P. BOUYGUES, and C. FAVERET. *Presse médicale* [*Presse méd.*] 67, 1630-1633, Sept. 26, 1959. 2 figs., 13 refs.

The authors, writing from the Hôpital Saint-Joseph, Paris, consider that the existence of a heredo-familial form of amyotrophic lateral sclerosis (A.L.S.) is now well established, this view being reinforced by the recent discovery in the Chamorro tribe in the Island of Guam of an incidence of the disease nearly 100 times that in an average general population. To the 40 family trees previously published the authors add a further 2 personally investigated genealogies showing multiple cases of the disease. Each of these 42 familial groups of cases stemmed from one adult patient with A.L.S., which could often be traced through three or even four generations. After rejecting 13 family histories because of inadequate data the authors discuss the remaining 29 families, comprising a total of 121 cases.

In adult patients the symptoms fall into three groups. (1) The classic sign of fibrillation in the muscles, typically starting in the upper limbs, being roughly symmetrical, and sparing the trunk and neck muscles. (2) Pyramidal signs, in some cases amounting to no more than exaggerated tendon reflexes; the Babinski reflex is extensor in just over half these cases. (3) The bulbar syndrome, with labio-glosso-pharyngeal paralysis. Motor branches of the 5th cranial nerve may be involved, but the upper branches of the 7th nerve and all branches of the 6th are spared; death occurs from respiratory paralysis. No sensory or cerebellar symptoms have been described.

The onset in 40 to 45% of these cases is manifested by upper limb amyotrophy, in 25% by bulbar palsy, in 5 to 10% by pseudo-polyneuritis, and in 10 to 20% by pyramidal involvement. The mean age at onset was shown to be 46.8 years and at death 49.5 years. Of the 121 patients studied, 62% were men and 38% women. The incidence of the typical adult disease in general populations elsewhere in the world is about 1.4 per 100,000 (though if the families in each case were studied it might prove to be nearer to 4 per 100,000), but in Guam the incidence is 420 cases per 100,000 population, that is, about 100 times higher, as stated above.

The authors discuss the question of whether the disease has ever occurred in children, concluding that those neurological cases identified among affected families resemble more the amyotrophic forms of the Strumpell-Lorrain type of familial spastic paraplegia. Nevertheless these juvenile forms are regarded as aberrant examples of the adult sporadic A.L.S. They suggest that the disorder is transmitted by a dominant gene with incomplete penetration. Occasionally a generation is skipped; this observation and the fact that the juvenile type is not true to type the authors attribute to multifactorial aetiology. In addition to the specific gene some exogenous factors seem to be necessary to precipitate the classic or sporadic form of the disease.

William Hughes

DEMYELINATING DISEASES

988. A Study of Coagulation Factors in Blood and Spinal Fluid in Multiple Sclerosis

S. D. ALBRIGHT III, H. G. KUPFER, and D. R. KINNE. *A.M.A. Archives of Neurology* [A.M.A. Arch. Neurol.] 1, 315-326, Sept., 1959. 38 refs.

In a small series of 10 patients with disseminated sclerosis, in 9 of whom the disease was progressive, the authors studied the coagulation and other properties of blood and cerebrospinal fluid (C.S.F.). The following values were found to be substantially normal: haemoglobin concentration; haematocrit reading; clotting time; erythrocyte and leucocyte counts and differential counts; platelet count; prothrombin, Factor V, and Factor VII concentrations; partial prothrombin time; fibrinogen level (moderately raised in one case in which the disease was severe and rapidly progressive); thromboplastic activity of the C.S.F. both with normal and with the patient's own plasma; and serum platelet-like activity.

Certain features, however, were found to be abnormal. For example, in 9 cases platelets were overlarge and/or irregular in shape; nevertheless thromboplastin formation of these cells was normal in each instance. There was a positive reaction to the capillary fragility test in 8 patients and a negative reaction in 2, both negroes. Increased capillary fragility was not necessarily associated with a corresponding change in the platelet morphology and the platelet counts were within normal limits.

The authors briefly discuss the reported work of others who consider that vascular coagulation factors are concerned in the pathogenesis of the plaque of disseminated

sclerosis, a hypothesis to which they clearly cannot subscribe on the basis of the present findings.

J. B. Cavanagh

989. Critical Examination of the Isolation of Spirochaetes in Disseminated Sclerosis, (Kritische Nachprüfung der Spirochätenbefunde bei Multipler Sklerose) A. HOFMANN and G. SCHALTENBRAND. *Münchener medizinische Wochenschrift* [Münch. med. Wschr.] 101, 1589-1592, Sept. 18, 1959. 6 figs., 21 refs.

The finding of spirochaetes in the tissues of patients with disseminated sclerosis, first reported by Kuhn and Steiner in 1917, received a certain amount of confirmation from the work of Adams *et al.* in 1925, but there was no general acceptance of the hypothesis that a spirochaete was the aetiological factor in this disease. The question was reopened by Ichelson (*Proc. Soc. exp. Biol. (N.Y.)*, 1957, 95, 57; *Abstr. Wld Med.*, 1958, 23, 5), who used a new culture method and recorded the presence of spirochaetes in cultures of cerebrospinal fluid (C.S.F.) from 59 out of 76 clinical cases of disseminated sclerosis. Phase-contrast and dark-ground illumination were used for the examination of the cultures, and the spirochaetes were stated to range from 10 to 22 μ in length and 1 μ in thickness.

At the University Neurological Clinic, Luitpold-krankenhaus, Würzburg, the present authors have made a critical examination of these results, using various techniques, including the culture method recommended by Ichelson. A total of 208 specimens of C.S.F. from patients with various diseases were examined, and spirochaetal forms were seen in 9 cases as indicated in the following table.

Disease	Number Examined	Spirochaetal forms Observed
Disseminated sclerosis ..	60	1
Disseminated sclerosis (suspected) ..	13	2
Cerebrospinal syphilis ..	11	—
Various degenerative conditions ..	55	2
Tumours ..	8	2
Infections of the central nervous system ..	23	1
Head injuries ..	4	—
Cerebrovascular accident ..	9	1
Rheumatism and other toxic disorders ..	9	—
No organic neurological disease ..	11	—
Undiagnosed ..	5	—
Total ..	208	9

The methods employed in the investigation of these fluids were: culture on Ichelson's medium, 104 cases with one positive result; direct examination, 181 cases, and examination of the centrifuge deposit, 38 cases, with no positive result; and examination after Sayk-Steger's method of sedimentation, with 8 positive results. It is perhaps significant that this last method involves the longest manipulation of the fluid.

The authors are of the opinion that all the spirochaetal forms observed were artefacts resulting from the scratching of microscope slides and cover slides, and were probably glass shavings.

Edward Hindle

Psychiatry

990. Cases of Attempted Suicide Admitted to a General Hospital

J. A. HARRINGTON and K. W. CROSS. *British Medical Journal* [Brit. med. J.] 2, 463-467, Sept. 19, 1959. 16 refs.

The authors of this paper from the Uffculme Clinic and the University of Birmingham point out the difficulty of obtaining representative samples of suicides and the danger of over-simplifying concepts about the cause of suicide. They have analysed a series of 102 cases of attempted suicide obtained from the wards of a large general hospital. The agents used were barbiturate in 39 cases, aspirin in 23, other poisons in 18, carbon monoxide in 13, and miscellaneous methods such as cutting and strangulation in the remainder. Living alone was not a feature of these cases, but the authors suggest that discovery and therefore resuscitation are more likely when others live in the same house. Unemployment was a possible factor in only one case.

Nearly half of the patients had a history of previous psychiatric breakdown and 20 of previous suicidal attempts. In 42 cases the precipitating cause was interpersonal conflict, which in the present investigation proved much more important than loneliness. The familiar motives of guilt, loneliness, aggression, and appeal were all found. There were no clear-cut gradations of seriousness of the attempt, there being a continuum between the trivial and the determined. In 62 instances the patient was glad that the attempt had failed. Depressives tended to commit suicide alone, but attempts made in a spirit of anger or revenge after a quarrel often took place either in the presence of the person concerned or in an adjacent room. Half the patients had depressive disorders, 11 were psychopaths, and 6 were chronic alcoholics. There was a clear-cut group classified under the heading of "situational maladjustment", a half-hearted attempt being made with the motive of applying moral blackmail to obtain the capitulation of the other person concerned; the patients in this group were all emotionally immature. There were no cases of anxiety neurosis.

The authors find no justification for assuming that every person attempting suicide is psychiatrically ill, but nevertheless about three-quarters of their patients needed some form of psychiatric treatment. They point out the desirability of psychiatric assessment in all cases of attempted suicide and stress the importance of the early recognition of depression.

Gavin Thurston

991. Emotion and Blood-pressure

G. INNES, W. M. MILLAR, and M. VALENTINE. *Journal of Mental Science* [J. ment. Sci.] 105, 840-851, July [received Nov.], 1959. 5 figs., 10 refs.

The authors of this paper from the University of Aberdeen have studied changes in the blood pressure occurring during a discussion of the patient's life experi-

ences and also during breath-holding and a mental arithmetic test. The subjects studied were 25 patients with hypertension of pregnancy, 13 psychoneurotics with labile or normal blood pressure, 29 patients with essential hypertension, and a control group of 40 healthy maternity patients recently delivered.

It could not be established that revived anger or fear or the degree of repression thereof were correlated with blood-pressure changes, but there was a slight positive correlation between the pressor response and discussion of the husband by female patients and the discussion of illness. In a study of continuous blood-pressure recordings it was found that hypertensive epochs tended to be associated with a significantly greater number of self-references and a greater output of syllables per 10 seconds than were hypotensive epochs. The mean highest readings recorded during interviews was higher than those during breath-holding. The highest reading recorded, however, was found to be due to an unexpressed desire to micturate.

K. W. Todd

MENTAL DEFICIENCY

992. The Size of Mental Defective Boys

G. DUTTON. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 34, 331-333, Aug. [received Oct.], 1959. 12 refs.

A study of the height, weight, and skeletal development of mentally defective boys is reported from Botleys Park Hospital, Chertsey, Surrey. The patients (aged 5 to 18 years) were divided into four groups: (1) those with organic lesions of the brain (31); (2) those whose physical size was normal for age ("non-pathological" group) (16); (3) patients whose height was diminished by more than a year of height age ("metabolic" group) (22); and (4) mongols (50).

Height was measured to the nearest $\frac{1}{8}$ inch (3.2 mm.) and weight to the nearest $\frac{1}{4}$ lb. (227 g.) on a beam balance. Skeletal development was recorded from a single radiograph of the left wrist and hand. Comparison of the means of the developmental quotients for height, weight, and skeletal growth showed that the mongols and the metabolic group were similar as regards weight and height, while these values in the other groups fell within the normal limits of 80 to 120. Of the metabolic group, 16 (72.7%) showed a skeletal development depressed more than 2 S.D. below the mean, whereas of the other groups taken together, only 25.8% showed similar retarded skeletal development.

The author has previously shown that the metabolic group are immature in respect of urinary excretion of steroids and of non-protein nitrogen and the serum alkaline phosphatase level, whereas patients in the non-pathological group are normal in these respects. He

therefore considers that there is a metabolic type of patient "characterized by retarded skeletal development, depressed height age, and biochemical immaturity", which is distinct from other types of mental defective.

G. de M. Rudolf

993. Appearance of Parkinsonism in Mentally Defective Patients Treated with "Dartalan", with the Occurrence of Oculogyric Crises in Identical Twins

W. A. HEATON-WARD, W. H. K. CARPENTER, and J. JANCAR. *British Medical Journal* [Brit. med. J.] 2, 407-408, Sept. 12, 1959. 2 refs.

In this paper from the Stoke Park Hospital Group, Bristol, the authors describe their experience of administration of "dartalan", a phenothiazine derivative, for the control of behaviour disorders in mental defectives. Of 31 mentally defective patients (19 female and 12 male, aged 13 to 45 years) without evidence of extra-pyramidal involvement, Parkinsonism developed in 15 (11 female and 4 male) during treatment with dartalan in a daily dosage of 20 to 60 mg. The symptoms of Parkinsonism were treated by administration of 50 mg. of "disipal" three times a day, the dosage of dartalan remaining unchanged.

It is suggested that the reason for the high incidence of Parkinsonism is that in the mental defective the basal ganglia are already damaged, although insufficiently so for signs of Parkinsonism to develop, so that dartalan may cause these signs to appear more readily than in psychotic or non-psychotic patients.

G. de M. Rudolf

994. Syphilis as a Cause of Mental Deficiency

J. M. BERG and B. H. KIRMAN. *British Medical Journal* [Brit. med. J.] 2, 400-404, Sept. 12, 1959. 11 refs.

It has been suggested that with the fall in the incidence of syphilis in Great Britain mental deficiency due to this disease should become less common. At the Fountain Hospital, London, the history and serological findings over a 12-year period in respect of 1,900 mental defectives, mainly idiot and imbecile children, were analysed, and in 12 of them syphilis was considered to be the cause of the mental deficiency. Of the 12 patients, 8 had congenital syphilis; the remaining 4 showed no evidence of infection but all 4 had a history of maternal syphilis. All the children were born before 1950 and 7 of the 12 were illegitimate. If the mental deficiency in all 12 cases was attributed to congenital syphilis then the incidence was 0.6%; if, however, congenital syphilis was considered to be the cause only in those cases in which there were clinical signs of changes in the cerebrospinal fluid the incidence was 0.2%. The authors point out that the rise in the incidence of acquired syphilis associated with the Second World War does not appear to have been paralleled by a rise in the incidence of congenital syphilis. They emphasize the need for repeated serological examination; in all the cases in their series a positive reaction to serological tests for syphilis was obtained on more than one occasion.

[Much in this article is common knowledge.]

G. de M. Rudolf

ORGANIC DISORDERS

995. Cerebral Circulation in Patients Suffering from So-called Presenile Cerebral Atrophy. (Kreislaufanalysen (Hirndurchblutungsmessungen) bei sogenannten präsenilen Hirnatrophien)

H. LENNARTZ. *Fortschritte der Neurologie, Psychiatrie und ihrer Grenzgebiete* [Fortschr. Neurol. Psychiat.] 27, 469-480, Aug., 1959. 5 figs., 16 refs.

Using the method of Kety and Schmidt, the author measured the cerebral circulation in 30 patients with presenile cerebral atrophy at the Psychiatric and Neurological Clinic of the University of Hamburg. All had signs of mental abnormality and pathological findings on air encephalography. [There is a suggestion that they were selected because of the latter.] Reduction of the cerebral circulation and oxygen consumption was found in 20 cases, together with increased vascular resistance and increased mean pressure in the cerebral arteries. The degree of abnormality found did not correspond regularly with the degree of hydrocephalus, but tallied well with the clinical severity of the case. The author concludes that this type of cerebral atrophy is the consequence of an organic process within the cerebral blood vessels.

W. Mayer-Gross

996. The Physiological Basis of the Treatment of Delirium Tremens

H. KRYSTAL. *American Journal of Psychiatry* [Amer. J. Psychiat.] 116, 137-147, Aug., 1959. 6 figs., 44 refs.

During the 3 years 1954-6 700 patients suffering from delirium tremens were admitted to the Detroit Receiving Hospital, 82% being male. The mean duration of the illness, if uncomplicated, was 3 days.

In 45 consecutive cases in which there were no signs of liver failure or ascites the serum electrolyte levels were investigated. It was found that the average sodium level tended to be below normal limits, but there was a wide variation which was partly due to the administration of intravenous saline. The average potassium level tended to be in the high normal range. Magnesium values were low or within normal limits, none being high because no magnesium was administered therapeutically to these patients. Haematocrit readings tended to be high on the first day, but quickly fell to normal levels.

The author speculates on the physiological and emotional components of delirium tremens and recommends a "specific" treatment that takes account of them. This includes a peptic-ulcer regimen with vitamins to counter gastritis; the replenishment of depleted water and electrolyte levels; the administration of deoxycortone acetate as a precaution against brain swelling and of antibiotics as protection against infections; and "reality-orientated" psychotherapy to deal with the patient's terrifying aggressive wishes. He counsels against the use of cortisone or paraldehyde.

Among the 700 patients there were 16 deaths: 5 were due to infections which did not respond to antibiotics, 5 due to brain swelling, and 6 due to causes unconnected with delirium tremens. There was no fatality among the 69 patients treated by the methods advocated by the

author, who claims statistical significance for this result [but it is impossible to accept this claim].

F. K. Taylor

SCHIZOPHRENIA

997. **Heller's Disease and Childhood Schizophrenia**
N. MALAMUD. *American Journal of Psychiatry* [Amer. J. Psychiat.] 116, 215-218, Sept., 1959. 3 refs.

In this paper from the Langley Porter Psychiatric Institute, San Francisco, the problem of differentiating organic from psychogenic symptoms in childhood is discussed and the cases of 6 children with organic brain disease who were diagnosed clinically as having childhood schizophrenia are described. The indiscriminate grouping of such aetiologically different conditions as Heller's disease, childhood psychosis, childhood schizophrenia, autism, and mental defect under the name of "atypical development" is criticized as being misleading. The condition most likely to be confused with childhood schizophrenia is Heller's disease in which, beginning with symptoms of a character disorder at about 3 or 4 years, there is a slow mental regression followed by motor disturbances, possibly speech loss, and finally idiocy. Its organic nature was demonstrated by Corberi, who found "diffuse lipoid degeneration of the ganglion cells" in brain biopsies. This suggests a relationship with Tay Sachs' disease, though there are no retinal changes.

In the cases described the 6 children consisted of 3 pairs of siblings. The diagnosis in the first 4 was of "amaurotic family idiocy without amaurosis". In 2 cases this condition was recognized only at necropsy. Ballooning of the nerve cells with lipoid material with the staining properties of fatty acids was observed to be widespread in the cerebral cortex and spinal cord. In both these children the onset of illness had occurred at 3 years with severe behaviour problems. The first had marked neurological features from early in the illness; the second, who died at 7, showed no neurological features, but was severely retarded, with an I.Q. of 33. Both children had a sibling with a similar progressive illness combining behavioural disorder and motor disability. The electroencephalogram (EEG) in 3 of these cases was abnormal. In the other 2 children, siblings who both died, the findings at necropsy were those of a primary degenerative disease. This was confined to the corpus Luysi, the mamillary bodies, and the mamillothalamic tract, where dense reactive fibrillary gliosis was found. The illness began in both at school age with progressive intellectual impairment; both were hyperkinetic and in both cases the EEG was abnormal.

The author considers that these 6 cases were examples of Heller's disease. The diagnosis during life of childhood schizophrenia was the result of neglecting the neurological features, including the EEG findings, and failing to recognize that what were regarded as mannerisms and tics were really choreiform movements and ataxia. This separation of organic factors and personality disturbance in these cases is criticized, as is the term Heller's disease, which is considered to be insufficiently precise.

J. S. Bearcroft

998. Slowness in Schizophrenia

A. HARRIS and M. METCALFE. *Journal of Neurology, Neurosurgery and Psychiatry* [J. Neurol. Neurosurg. Psychiat.] 22, 239-242, Aug. [received Oct.], 1959. 12 refs.

Patients with all forms of mental illness tend to be slower than normal subjects. The authors, working at the Bethlem Royal and Maudsley Hospitals, London, have studied the influence of various factors such as length of illness, previous physical treatment, and present clinical state on the speed of performance of the two versions ("stressed" and "unstressed") of the Nufferno speed test in 53 schizophrenic patients with a mean age of 30 (range 19 to 56) years and a mean I.Q. of 107, of whom 23 had been ill for less than one year, 2 for over 20 years, and the remaining 28 for intermediate periods.

The test scores showed (1) that the longer the illness, the slower the performance, but this relationship was not statistically significant and applied only to those who showed inappropriate affect. (2) Patients who had had previous physical treatment tended to be slower than those who had not, but again results were not statistically significant. (3) Clinical improvement resulted in some very slight improvement in speed, but was investigated in only 6 patients, most of the others having previously had physical treatment. Lastly, in assessing the predictive value of the test 37 patients in whom the outcome of the illness was in doubt (rejecting those whose condition had been static for many years) were interviewed one year after testing and assessed on clinical and social criteria, their test results not being known to the investigator. Higher speeds in the unstressed test were associated with a more favourable outcome, but not at a statistically significant level. The "stress-gain" score, that is the difference between the scores in the stressed and unstressed versions of the test, differentiated at a satisfactory level of significance between "independent" patients and those still in hospital; but when the most appropriate "cutting-score" was used to discriminate between the two groups 28% were wrongly classified. The trends of results of this study were mostly in the expected directions, but none were significant.

F. E. Kenyon

999. The Use of an Object Sorting Test in Elucidating the Hereditary Factor in Schizophrenia

N. MCCONAGHY. *Journal of Neurology, Neurosurgery and Psychiatry* [J. Neurol. Neurosurg. Psychiat.] 22, 243-246, Aug. [received Oct.], 1959. 11 refs.

An investigation is reported from St. Ebba's Hospital, Epsom, of Kallman's theory that a specific recessive gene is responsible for the transmission of schizophrenia and that the presence of the gene may be indicated in those who have successfully resisted the disease by the finding of schizoid personality changes. To this end both parents of 10 schizophrenic patients were tested by Rapaport's sorting test (with additions by Lovibond) in which everyday objects are sorted into appropriate groups and the reasons for the grouping explained by the subject. In scoring the test only the degree of irrele-

vance of the response is scored, no score (that is, no penalty) being given for either failure to see a relationship or for using concrete reasoning. The criteria of selection of the parents are stated, the two chief being that they were parents of a patient with thought disorder, here defined as "thinking which contains illogical, inappropriate or irrelevant associations", and that they themselves showed no apparent psychiatric illness.

The results were compared with those in a control group and showed that in each of the 10 cases at least one of the parents had a score above 6, a score which significantly correlates with the presence of clinically observed thought disorder in schizophrenics. Application of the χ^2 test (with Yates's correction for small numbers) showed that the probability of the parents and control subjects having come from the same population was less than 0.1% ($P < 0.001$). Thus the scores of parents of schizophrenic patients with thought disorder differ from those of normal subjects in the same direction as do those of the patients themselves. In discussion it is suggested that if this sorting test does provide an objective measure of certain aspects of schizoid personality, then the finding of such a score in at least one of the parents of each of the present patients supports Kallman's theory. The fact that a significant score was present in both parents of 2 of the patients might appear to be more suggestive of dominant inheritance, but this discrepancy could have been due to the selection of patients, since only those with thought disorder were included in the study.

F. E. Kenyon

1000. The Treatment of Schizophrenic Out-patients with Promazine and Reserpine

D. M. ENGELHARDT, N. FREEDMAN, L. D. HANKOFF, B. S. GLICK, H. E. KAYE, and J. BUCHWALD. *Psychiatric Quarterly [Psychiat. Quart.]* 33, 102-114, 1959. 3 refs.

The authors report (from New York State University Downstate Medical Center, Brooklyn), the results of ataractic treatment of 35 schizophrenic out-patients, the majority of whom showed "severe paranoid thought processes, obsessive thinking, and affective withdrawal". Over a period of at least 2 months 20 of the patients received promazine, 50 to 400 mg. daily by mouth, and 15 reserpine, 0.5 to 4 mg. daily, the two groups being closely matched for age and sex; each patient acted as his own control, the results during the treatment period being compared with those during a preceding period when a placebo was given. Psychotherapy was avoided as far as possible during the trial. Three forms of evaluation were employed, a 54-item psychiatric rating scale adapted from the Lorr scale, an "abbreviated clinical rating scale" of 15 items dealing with major areas of psychopathology, which was completed by the psychiatrist after each visit, and a "comparative global evaluation" made at the patient's last visit, which consisted of a unitary criterion of improvement in five classes ranging from "definitely worse" to "definite improvement".

Definite improvement was shown by 8 (40%) of the patients taking promazine and by 7 (47%) of those taking reserpine, three specific areas of improvement

being noted, an increase in warmth in interpersonal relationships, a decrease in paranoid projection, and a decrease in affective withdrawal; the first of these changes occurred during the placebo period. There was some evidence, not statistically significant, that promazine acted more rapidly than did reserpine. About 6 weeks of treatment was required for the drugs to reach equal effectiveness. No serious side-reactions were encountered, but the patients who eventually showed definite improvement with promazine tended to show specific transitory side-effects. The latter observation, taken together with the lack of results in the placebo period, suggests that the changes observed were specific to the drug treatment.

F. E. Kenyon

1001. The Administration of BAS, 5-HTP, and Marsilid to Schizophrenic Patients

A. FELDSTEIN, H. FREEMAN, J. M. HOPE, I. M. DIBNER, and H. HOAGLAND. *American Journal of Psychiatry [Amer. J. Psychiat.]* 116, 219-221, Sept., 1959. 2 figs., 8 refs.

The hypothesis that schizophrenia might be related to either a deficiency or an excess of serotonin in the brain was first put forward by Woolley and Shaw in 1954 (*Brit. med. J.*, 2, 122). To test the corollary that by the administration of 5-hydroxytryptophan (5-HTP), the precursor of serotonin, to schizophrenic patients the illness might be improved or worsened 5 male chronic schizophrenic patients at the Worcester State Hospital, Massachusetts, were given 5-HTP by intramuscular injection. At the same time they were given 1-benzyl-2,5-dimethyl-serotonin (BAS) in order to protect them against the gastro-intestinal effects of an excess of serotonin, while 2 patients also received "marsilid" (iproniazid) in order to inhibit the monoamine oxidase destruction of serotonin.

In the first study 4 patients received 100 mg. of BAS by mouth daily for 2 weeks after a control period of one week. 5-HTP was then added in a dosage of 15 mg. twice daily for 2 further weeks, followed by another control period of one week. In the second study 3 of the same patients and one other received 100 mg. of 5-HTP daily with BAS, and 2 of them also received 100 mg. of marsilid daily, the period of treatment being 3 weeks. No change of behaviour was noted with any of these combinations of drugs, which confirms the previous findings of Woolley (loc. cit.) and casts doubts upon the hypothesis.

Examination of the urine of these patients for 5-hydroxyindole acetic acid (5-HIAA) failed to show the expected increase after the administration of BAS and 5-HTP, and BAS alone caused no change in the urinary 5-HIAA excretion pattern in these patients. It was thought likely that BAS causes a metabolic block and that the absence of an increase in 5-HIAA excretion was not due to the absence in schizophrenics of any specific enzyme converting 5-HTP to 5-HIAA. Chromatographic examination of the urine showed that serotonin was present when both BAS and 5-HTP were given, but not while BAS alone was being given or during the control period. It would therefore appear that BAS

functions as a monoamine oxidase inhibitor, preventing the conversion of 5-HTP to 5-HIAA so that an accumulation of serotonin in the urine occurred.

J. S. Bearcroft

1002. Production of High-energy Phosphate Bonds in Schizophrenia

J. S. GOTTLIEB, C. E. FROHMAN, P. G. S. BECKETT, G. TOURNEY, and R. SENF. *A.M.A. Archives of General Psychiatry* [A.M.A. Arch. gen. Psychiat.] 1, 243-249, Sept., 1959. 4 figs., 5 refs.

As part of a series of biochemical investigations being carried out at Wayne State University College of Medicine, Detroit, into the intracellular formation and utilization of the energy set free in glycolysis or the conversion of adenosinetriphosphate (ATP) into adenosinediphosphate (ADP) the authors have examined the question whether these intracellular processes are disturbed in schizophrenic patients. For this purpose they have investigated these processes in the erythrocytes of three groups of male patients aged 18 to 35, composed as follows: (1) 10 non-schizophrenic patients who served as a control; (2) 10 patients with acute schizophrenia, that is, with symptoms of less than 2 years' duration; and (3) 10 with chronic schizophrenia (symptoms of more than 4 years' duration), the three groups being matched for diagnosis and physical status. During the study the patients' diet was controlled.

After a 5-day stabilization period at a basal level of activity 25 ml. of blood was taken from each patient and incubated for one hour with 0.5 mc. of radioactive phosphorus in the form of phosphoric acid. The acid-soluble phosphates were then removed from the erythrocytes by trichloroacetic acid and precipitated with barium. By ion-exchange chromatography the following phosphates were separated, ATP, ADP, adenylic acid, and fructose-1:6-diphosphate (F1:6P), their amounts determined, and also their radioactivity assessed in order to evaluate the extent of specific chemical activities which had taken place in the various compounds, it having been shown that the greater the specific activity, the greater the incorporation of radioactive phosphates. A second similar investigation was carried out a week later, but this time half an hour after the intramuscular injection of 10 units of insulin.

It was found that the amounts of ATP did not significantly differ in the three groups of patients. Under basal conditions the specific chemical activity of ATP was highest in chronic schizophrenics and lowest in these patients after insulin. The most clear-cut results were obtained in the case of F1:6P. Under basal conditions the two schizophrenic groups showed a specific activity of this phosphate significantly greater than that in the control subjects ($P < 0.01$ in both cases). The specific-activity response to insulin was significantly different in the control group from those of both schizophrenic groups ($P < 0.05$ and $P < 0.001$, respectively).

The authors admit that the interpretation of these results is difficult, but claim nevertheless that the findings support the general hypothesis that the formation and utilization of energy is disturbed in schizophrenic patients.

F. K. Taylor

1003. Indoluria in Schizophrenia. I. Statistical Study and Investigation of Hepatic Function

A. D. FORREST. *Journal of Mental Science* [J. ment. Sci.] 105, 674-684, July [received Nov.], 1959. 43 refs.

The investigation reported in this paper from the University of Edinburgh was based on the hypothesis that tryptophan metabolism plays a role in the aetiology of some schizophrenic illnesses and that this metabolism may be affected by diet, intestinal flora, and the functions of the intestines, liver, and probably the adrenal glands. To test this hypothesis the author carried out (a) a statistical comparison of indoluria in schizophrenic patients and other groups of subjects, and (b) liver function tests on schizophrenic patients.

For the statistical comparison of indoluria he examined 7 groups of subjects with a total membership of 285. [Unfortunately, most of these groups were not comparable in such significant aspects as age, diet, medication, fluid intake, and so on. A statistical comparison of indoluria alone is worthless under these circumstances.] An early morning specimen of urine was examined, a two-way ascending chromatographic method of indole assessment being employed. Excess indole excretion (according to defined criteria) occurred in 32 (52.5%) and in 22 (44%) of 50 non-schizophrenic psychotic males. This difference was not statistically significant. Among 25 normal males, however, excess indole excretion was found in only 2 cases (8%) and the difference between this group and the two psychotic groups combined was significant at the 5% level. In comparable groups of female patients and normal subjects on the other hand the differences, both between the two psychotic groups and between these groups and the normal group, were too small to have any statistical significance. In the other groups investigated—50 "medical subjects" and 25 mental defectives—the incidence of excess indole excretion was approximately 30%. The author considers that "the results of this study indicate that within the group designated schizophrenic there is a subgroup excreting an excess of indole substances". [This could be said of the other groups as well.]

Liver function was assessed in 29 male and 19 female schizophrenic patients by means of the cephalin-cholesterol flocculation test. The results were not significant.

F. K. Taylor

1004. Indoluria in Schizophrenia. II. Chromatographic Study on 40 Schizophrenic and 10 Normal Subjects

A. D. FORREST. *Journal of Mental Science* [J. ment. Sci.] 105, 685-692, July [received Nov.], 1959. 16 refs.

Continuing his investigation of indoluria in schizophrenia [see Abstract 1003] the author studied differences in the types of indoles excreted by two groups of subjects: (a) 25 male and 15 female schizophrenic patients with a mean age of 43.5 ± 7.5 years and a mean length of illness of 17.2 ± 7.6 years; and (b) 10 normal persons with a mean age of 26.3 ± 8.4 years.

Concentrates made from early morning urine were examined by a two-way chromatographic method, particular attention being paid to a spot described as "quickly fading blue" which appeared identical with

those reported by Riegelhaupt (*J. nerv. ment. Dis.*, 1958, 127, 228), by Rodnight and Aves (as "U2") (*J. ment. Sci.*, 1958, 104, 1149), and by Buscaino and Stefanachi (*A.M.A. Arch. Neurol. Psychiat.*, 1958, 80, 78) in schizophrenic urine, the identity of which is uncertain. This spot occurred in 57.5% of the specimens from schizophrenics and in 30% of those from the normal subjects. No correlations were found between indole excretion, age of the patient, length of illness, and other diagnostic features.

F. K. Taylor

TREATMENT

1005. Trifluoperazine in Psychoneurotic Outpatients

E. S. GODDARD. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] 81, 467-470, Sept. 15, 1959. 6 refs.

At Victoria Hospital, London, Ontario, trifluoperazine, a phenothiazine derivative which has been found to increase attention, vigilance, and concentration in psychotics in withdrawn states, was given to 72 non-psychotic patients. Generally the dosage was 1 or 2 mg. 3 to 4 times a day initially, reduced within 1 or 2 weeks to 1 mg. twice a day. The average duration of treatment was 4 weeks. By the second week of treatment patients were less irritable and said they were eating and sleeping better. Physician-patient rapport improved and patients became accessible to psychotherapy. Of the 72 patients, 52 were able to return to work and found adjustment to stress easier. The beneficial effects of the drug continued after administration ceased. The results were not encouraging in obsessive compulsive types, in patients suffering from agitated depression, or in schizophrenia.

Side-effects were headache and drowsiness, but the author found that the unfamiliarity of the relaxed state to the anxiety neurotic led patients to mistake this for drowsiness. A gain in weight was observed in 6 patients. There was no evidence of hypotension, jaundice, or blood dyscrasia.

Gavin Thurston

1006. A Comparison of Perphenazine ("Fentazin"), Sodium Amylobarbitone and a Placebo in Anxious and Depressed Out-patients

J. M. HINTON. *Journal of Mental Science* [*J. ment. Sci.*] 105, 872-877, July [received Nov.], 1959. 10 refs.

At the Maudsley Hospital, London, 27 out-patients with anxiety and depression of 2 weeks' to 7 years' duration, selected as probably suitable for tranquillizer treatment, were given perphenazine, 8 mg. a day, sodium amylobarbitone 4 grains (0.26 g.) a day, and a placebo of lactose for 2 weeks each in random order, a double-blind technique being used. The effect of the treatment was assessed every one or 2 weeks during the trial both by the physician and by the patient, and at the end of the trial the patient was asked to rank the three periods of treatment in order of preference.

The patients' assessments showed a significant improvement in symptoms during the 6 weeks of treatment, but failed to differentiate to a significant degree between the treatments. The physician's assessment, however, showed significantly greater general improvement with

the two active drugs than with the placebo; both had an equal effect on anxiety, but only perphenazine improved depression significantly more than the placebo. There were no serious side-effects.

K. W. Todd

1007. A Clinical and Biochemical Study of a Trial of Iproniazid in the Treatment of Depression

C. M. B. PARE and M. SANDLER. *Journal of Neurology, Neurosurgery and Psychiatry* [*J. Neurol. Neurosurg. Psychiat.*] 22, 247-251, Aug. [received Oct.], 1959. 1 fig., 26 refs.

At the Maudsley and Royal Free Hospitals, London, the authors carried out a controlled trial of iproniazid on 50 patients with depression, the aims being to test the efficacy of the drug, to determine whether those who responded could be differentiated clinically or biochemically from those who did not, and to determine the mode of action of the drug. Iproniazid was given by mouth in doses of 150 to 450 mg. per day for periods ranging from 2 to 40 weeks, a placebo being substituted in certain cases for various periods. The degree of depression was assessed weekly by the registrar, who did not know whether drug or placebo was being given. A specific response to the drug was recorded if patients initially improved with the drug, relapsed when given the placebo, and improved again on resuming the drug; if there was improvement with the drug but no relapse with the placebo it was recorded as "coincidental" improvement.

Results showed that 26 out of the 50 patients improved, 12 of these responding to the drug and 14 showing "coincidental" improvement; no improvement was noted in 24 cases. In those who responded the improvement did not usually start until the 2nd or 3rd week, and this period of delayed response was not shortened by increasing the dose. Side-effects were common, and one patient died from acute hepatic necrosis. Weekly determination of the serum glutamic oxalacetic transaminase activity (which was raised in 15 (30%) of the authors' patients) is suggested as a means of detecting early hepatic damage, any rise in this value being an indication for stopping treatment. Clinical assessment failed to differentiate those showing true improvement from those with coincidental improvement or no improvement. However, estimations of the urinary excretion of 5-hydroxyindoleacetic acid before giving iproniazid differentiated to a significant degree between those who subsequently responded and those who did not ($P < 0.05$).

As a confirmatory test patients known to respond to iproniazid were given intravenous injections of 5-hydroxytryptophan and 3:4-dihydroxyphenylalanine, both with iproniazid and without it, but neither clinical nor psychological assessment showed any alleviation of the depression. From this it is concluded that, within the limitations of the experiment, iproniazid does not act directly by increasing the brain concentrations of 5-hydroxytryptamine or of catechol amines. As no abnormal metabolites were found in urinary chromatograms, the theory (one of many) that iproniazid acts by diverting certain metabolites through alternative path-

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ways was not supported. As iproniazid produces marked benefit only in some patients it is suggested that the drug is not a general euphoriant, but acts only in patients whose depression is due to a specific metabolic abnormality.

F. E. Kenyon

1008. The Influence of Chlorpromazine on Pathologic Emotions and Sexual Unrest

F. F. FLACH and P. F. REGAN III. *Journal of Nervous and Mental Disease [J. nerv. ment. Dis.]* 129, 171-176, Aug. [received Oct.], 1959. 2 figs., 6 refs.

Chlorpromazine was given as an adjuvant to intensive psychotherapy to 142 patients at the Payne Whitney Psychiatric Clinic, New York. A number of psychopathological features, including sexual unrest, paranoid ideas, depression, fear, anxiety, hostility, and confusion, were assessed before, during, and after treatment. The drug was given by mouth in an average daily dose of 200 to 400 mg. [However, the duration of treatment is not defined and the results were not compared with those in patients receiving intensive psychotherapy without chlorpromazine.] There were significant variations in the effect of the drug on the different features. Moderate or marked improvement was seen in 30 (76.9%) of 39 patients with fear, 24 (66.7%) of 36 patients with sexual unrest, 13 out of 20 with confusion, 36 (62%) of 58 with paranoid features, and 46 (56.9%) of 81 with hostility. Less improvement was observed in respect of depression, anxiety, hypochondriasis, and depersonalization.

The authors conclude that in the patients studied much of the improvement was related to the ability of chlorpromazine to reduce sexual unrest, fear, and hostility. The drug did not appear to be effective in many conditions in which anxiety was a prominent feature.

B. M. Davies

1009. An Evaluation of the Therapeutic Use of Trifluoromazine in Mental Disease

B. E. ROEBUCK, J. L. CHAMBERS, and E. WILLIAMS. *Journal of Nervous and Mental Disease [J. nerv. ment. Dis.]* 129, 184-192, Aug. [received Oct.], 1959. 12 refs.

The value of "trifluoromazine" (fluopromazine) in the treatment of severe mental disease was studied at the Eastern State Hospital, Williamsburg, Virginia, in 124 patients, 109 of whom had a schizophrenic illness. The average duration of the mental disorder was 18 years. Fluopromazine, chlorpromazine, and a placebo were given for a period of 6 months to three groups of patients matched for age, sex, and diagnosis, a double-blind technique being used. It was found that in most cases 100 mg. of fluopromazine daily was adequate—this dosage being one-quarter or one-fifth of the dosage of chlorpromazine. Fluopromazine was less likely to cause side-effects than chlorpromazine, although in a dosage of over 200 mg. daily it rapidly produced Parkinsonian symptoms. It was at least as effective as chlorpromazine in bringing about improvement in the mental state of the patients, although 46 of the 79 patients receiving the active drugs did not improve during the 6 months.

Psychological tests were carried out before and after the period of treatment. In all treatment groups there was an improvement in the response to a significant majority of the tests, although the influence of test practice and of the increased attention these patients received during the trial period could not be allowed for.

B. M. Davies

1010. A Controlled Trial of Ethylcrotonylurea

J. P. BAKER. *Journal of Mental Science [J. ment. Sci.]* 105, 852-862, July [received Nov.], 1959. 4 figs., 5 refs.

At the Three Counties Hospital, Arlesey, Bedfordshire, a double-blind controlled trial of ethylcrotonylurea as a tranquillizer was carried out in comparison with chlorpromazine and a placebo. The dose of ethylcrotonylurea was 600 mg. daily for the first week and 1,200 mg. daily for the next 4 weeks, while that of chlorpromazine was 150 mg. daily for one week and 300 mg. daily for 4 weeks. The subjects were 25 female chronic schizophrenic patients who had been in hospital for 6 to 49 years. The results were assessed by means of the Parkside Behaviour Rating Scale.

It was found that the drug was safe and harmless in the dosage used, but that it did not improve behaviour significantly. Similarly chlorpromazine produced no improvement in behaviour, while it had the further disadvantage of causing undesirable side-effects in 30% of cases.

K. W. Todd

1011. Electroshock Therapy and Tranquilizing Drugs

S. LESSE. *Journal of the American Medical Association [J. Amer. med. Ass.]* 170, 1791-1795, Aug. 8, 1959. 18 refs.

In this paper from the Presbyterian Hospital, New York, and the Department of Neurology, Columbia University, the author summarizes his experience in the use of electric convulsion therapy (E.C.T.) with private patients over the past 4 years. He emphasizes the need for a careful initial physical examination; all the patients in his series who were over 35 underwent electrocardiographic and chest x-ray investigations before starting treatment. In most cases E.C.T. was modified with thiopentone followed by a muscle relaxant. Improvement was rated on a 4-point scale taking into account relief of symptoms and success in work and social relationships.

To 170 severely ill patients aged 22 to 74 who had failed to respond to various tranquilizing drugs given in adequate doses E.C.T. was given after discontinuation of drug treatment. The diagnosis in 94 cases was schizophrenia, in 61 involuntal melancholia, in 11 organic psychosis, and in 4 manic-depressive psychosis. The duration of illness before E.C.T. ranged from 8 years to 3 weeks. From 5 to 18 treatments were given. For at least 3 months after treatment 41% of the patients were symptom-free and working efficiently and happily, while 28% were able to work with some symptoms remaining. Recovery was related to diagnosis and to the duration of illness.

To a second group of 131 severely ill patients, comparable to the first in respect of diagnosis, duration of

illness, and failure to respond to tranquillizing drugs, E.C.T. was given in combination with a phenothiazine derivative (123 cases), reserpine (4 cases), or meprobamate (4 cases), which was given during treatment in the same dosage as before. The results did not differ from those obtained with E.C.T. alone. There was no evidence that the administration of the drugs reduced anxiety before treatment or abbreviated the organic psychoses following E.C.T., though between treatments they were of value in calming the severely agitated patient. The author did not find that the use of these drugs increased the danger of E.C.T.; prolongation of postconvulsive apnoea, untoward hypotensive reactions, and potentiation of the drugs used in modifying the E.C.T. were not observed. He concludes that the combined use of a tranquillizing drug with E.C.T. is seldom useful, but is not contraindicated in carefully selected agitated and excited patients in good physical health.

Christopher Wardle

1012. Predictive and Concomitant Variables Related to Improvement with Actual and Simulated ECT

N. Q. BRILL, E. CRUMPTON, S. EIDUSON, H. M. GRAYSON, and L. I. HELLMAN. *A.M.A. Archives of General Psychiatry* [*A.M.A. Arch. gen. Psychiat.*] 1, 263-272, Sept., 1959. 11 refs.

At the Veterans Administration Center, Los Angeles, 96 male patients aged 18 to 68 (mean 35) years were treated with real or simulated electric convulsion therapy (E.C.T.). The illness in these cases was "relatively chronic" but had a good prognosis; 66 of the patients had schizophrenic, 14 schizo-affective, and 16 depressive reactions and the duration of the illnesses varied from 1 month to over 10 years. In 67 cases the course of the illness had been intermittent. The aim of the study was to ascertain (1) whether certain variables were prognostic guides, and (2) what changes took place in patients who improved, and to this end 59 physiological, biochemical, psychological and psychiatric variables were measured before treatment and again one month afterwards. Improvement was estimated by (1) a global clinical evaluation; (2) a set of ratings based on interview and observation in the ward; and (3) a global assessment of changes in psychological test scores, an electronic computer being used in the statistical analysis of the data.

No variables were found that could be used as prognostic guides. Five variables showed a significant but low correlation (highest $r=0.28$) with improvement, these being duration of illness, age, motor retardation, autonomic instability, and a low calcium level in the cerebrospinal fluid. In the improved patients there was an increase in I.Q. level, ego defensiveness, motor speed, efficiency of psychological functioning, urinary creatinine and urinary uric acid content, and serum calcium level, while there was a decrease in the total serum catecholamine and fasting blood sugar levels and in uptake of radioactive iodine. Among the unchanged variables were: urinary inorganic phosphate level, urinary 17-ketosteroid excretion, and plasma protein-bound iodine level. The authors thus found it impossible to construct a "single rationale" that would explain their findings, and conclude that "the results do not make it possible

to predict with any degree of certainty which patients will improve under the experimental treatment conditions".

F. K. Taylor

1013. The Role of Prefrontal Lobe Surgery as a Means of Eradicating Intractable Anxiety

J. SLOCUM, C. L. BENNETT, and J. L. POOL. *American Journal of Psychiatry* [*Amer. J. Psychiat.*] 116, 222-230, Sept., 1959. 10 refs.

A consecutive series of 18 patients selected for prefrontal leucotomy for the relief of intractable anxiety over a period of 10 years is reported. The patients had resisted other therapeutic approaches and were chosen solely because of the intrapsychic tension, irrespective of other diagnostic category. All were severely disabled and had at some time been suicidal and 5, regarded as psychotic, had been in hospital for many years previously. All had had adequate electric shock treatment without lasting benefit, and all received supportive psychotherapy, physiotherapy, hydrotherapy, occupational and planned recreational therapy, and drugs, including tranquillizers and sedatives, during their stay in hospital. Frequent abreaction was attempted and projective tests were employed to assess the premorbid personality. From those considered suitable for operation a final selection was made by one independent consultant. Among the criteria for selection were an adequate premorbid personality, absence of any appreciable tendency to paranoid formulations or the release of aggressive behaviour, and a satisfactory emotional atmosphere at home, especially in respect of the attitude of the patient's spouse. All patients were kept in hospital for 60 days after operation to allow for educational contact with their families and because the immediate postoperative period is crucial to the eventual outcome. A carefully graduated postoperative regimen was observed and treatment with "dilantin" (phenytoin sodium) continued for a year.

A disappearance of the need for barbiturates and alcohol was a consistent result of operation. Of the 13 patients who were not psychotic, 12 have returned home to a well-adjusted independent existence without further treatment. A patient with ulcerative colitis, for whom colectomy was advised, has eaten what she likes for 4 years. Three patients with severe hay fever and asthma were improved. A fall in blood pressure was noted in the hypertensive patients.

The authors prefer a bimedian subfrontal operation. They have discarded topectomy in favour of lobotomy. The extent of the cut is critical, and any atrophic, arteriosclerotic, or other brain damage already present is mentioned as a limiting factor. They have reduced the operative mortality to *nil*, and the postoperative complications in this series were few. They make a strong claim for the use of prefrontal lobotomy in the treatment of intractable anxiety. They consider that the operation has fallen into disrepute, except in the major psychoses, because of the poor selection of patients, the extensive cuts used in the past, and the consequent excessive amount of emotional flattening.

J. S. Bearcroft

Paediatrics

NEONATAL DISORDERS

1014. **The Neonatal Icteric Form of Minkowski-Chauffard Disease (Hereditary Spherocytosis).** (La forme ictérique néonatale de la maladie de Minkowski-Chauffard)

M. LELONG, D. ALAGILLE, and J. DORMONT. *Archives françaises de pédiatrie* [Arch. franç. Pédiat.] 16, 577-598, 1959. 1 fig., bibliography.

In this paper from the Hôpital St-Vincent-de-Paul, Paris, 5 cases of congenital familial haemolytic disease (hereditary spherocytosis of Minkowski and Chauffard) producing neonatal jaundice are reported and are discussed together with 9 cases taken from the literature.

Jaundice usually appears within the first 24 hours, though it may be delayed for 2 or 3 days, and always introduces the possibility of iso-immunization. The Coombs test is negative and cold agglutinins should be excluded. While the family history was positive in all cases in the literature, no other case could be identified in the family in 3 of the authors' cases. The suggestion is made that this reveals either a mutation or an illegitimate birth. Treatment is discussed and exchange transfusion is recommended for hyperbilirubinaemia on the same basis as for haemolytic disease due to iso-immunization, as neurological sequelae have been reported. The authors consider that single repeat transfusions may be needed later in some cases, but that splenectomy should be postponed if possible for one year at least (though they were driven to this treatment in one of their cases at 4 months and in another at 7 months) in view of the danger of sepsis, and particularly of the occurrence of meningitis, after the operation. They point out, however, that this complication is not restricted to infants and children.

A. White Franklin

1015. Neonatal Hepatitis

R. G. SHORTER, A. H. BAGGENSTOSS, and G. B. LOGAN. *A.M.A. Journal of Diseases of Children* [A.M.A. J. Dis. Child.] 98, 359-369, Sept., 1959. 3 figs., 31 refs.

The authors describe the clinical and histological details of 7 cases of neonatal hepatitis seen at the Mayo Foundation between 1924 and 1957, together with one more case seen elsewhere in 1958, and compare the histological picture in these cases with that in 3 cases of congenital biliary atresia examined before the development of cirrhosis. They then discuss the significance of the findings in relation to the aetiology of neonatal hepatitis. Of the 8 patients, 7 were girls and only one was premature. Apart from a history of acute hepatitis in one of the mothers 3 years before the pregnancy, the family histories were not of significance. One infant died on the third day and was never jaundiced, but in all the others clinical jaundice appeared in the first month; the liver was enlarged in 6 cases and the spleen palpable

in 3. Four babies died within 8 months of the onset of symptoms, 2 had hepatic cirrhosis, and only one was in good health at the time of the last follow-up.

The histological changes in the liver were similar in all cases, the hepatic architecture being well preserved in all but one. The bile ducts were not dilated nor was bile pigment seen in them, while the blood vessels and lymphatic structures were essentially normal. In the portal tracts there was a little infiltration by inflammatory cells and fibroblastic activity with finger-like processes in the adjacent parenchymal tissue, this being especially obvious in the patient who died on the 3rd day. The most important changes were in the parenchymal cells, these showing scattered patches of necrosis with little inflammatory reaction, which, however, was never severe and eosinophilic necrosis was minimal. The most notable finding was the presence of giant cells which were 2 to 6 times the size of the normal parenchymal cells and contained an average of 9 nuclei of varying form, the cytoplasm being eosinophilic and the centre often structureless. Bile pigment granules were seen in the cytoplasm, sometimes aggregating to form microcalculi. The significance of these giant cells is uncertain—the eosinophilic cytoplasm suggests degeneration, but on the other hand the absence of mitotic figures in the nuclei does not rule out a regenerative process. None of the sections showed evidence of nodular regeneration. There were few intercellular bile plugs, any bile pigment present being mainly intracellular. In contrast, the cases of congenital atresia of the bile ducts showed more architectural damage, no giant cells, a predominantly central cholestasis, and large zones of eosinophilic necrosis.

The authors discuss the views of other workers on the aetiology of neonatal hepatitis, with particular reference to transplacental viral infection and blood-group incompatibility. They conclude that the disease may not be an entity, but that its clinical and histological features indicate a limited range of hepatic cellular response to a variety of stimuli.

F. P. Hudson

1016. The Administration of Sodium Glucuronate to Jaundiced Newborn Infants

J. H. DWYER and C. M. McCUE. *Pediatrics* [Pediatrics] 24, 400-403, Sept., 1959. 3 figs., 8 refs.

Sixteen cases of jaundice in the newborn period were treated with parenteral administration of sodium glucuronate. One case showed a decrease in concentration of indirect bilirubin in the serum, 2 cases showed a slight increase, and 13 cases showed no change during the entire observation period. Experimental evidence and clinical experience suggest that parenteral administration of sodium glucuronate does not enhance the formation of bilirubin glucuronide in the newborn infant. In the authors' experience, it has been an inefficient and

unreliable method of reducing the concentration of indirect bilirubin in serum. In our opinion exchange transfusion is still the only recognized therapeutic procedure for decreasing indirect bilirubin in serum in the newborn infant.—[Authors' summary.]

1017. The Effect of Triiodothyronine in Neonatal Hyperbilirubinaemia

M. H. LEES and C. R. J. RUTHVEN. *Lancet [Lancet]* 2, 371-373, Sept. 19, 1959. 18 refs.

The effect of triiodothyronine on the serum bilirubin level in full-term and premature infants was studied at Queen Charlotte's Maternity Hospital, London. The serum bilirubin level was determined daily in 100 infants with a birth weight of over 5½ lb. (2.5 kg.) who became jaundiced within 72 hours of birth. Triiodothyronine was given to alternate infants in a dosage of 5 or 10 µg. daily for 5 days after the jaundice was noted clinically. A group of 36 premature infants were also observed, alternate babies being given 5 µg. of triiodothyronine daily during the first 5 days of life.

The ratio of conjugated to total bilirubin was similar in the treated and control groups. The mean peak bilirubin level was the same in the controls and treated full-term babies, but the peak was reached 13 hours earlier in the latter. In the premature infants the time of the peak bilirubin level was the same in the treated and control groups, but the mean peak level was 2.6 mg. lower in the treated than in the control group. These differences are, however, so small that treatment with triiodothyronine does not provide an alternative method to exchange transfusion.

R. M. Todd

1018. Activity of Glutamic-oxalacetic Transaminase and Lactic Dehydrogenase in Cerebrospinal Fluid and Plasma of Normal and Abnormal Newborn Infants

M. LENDING, L. B. SLOBODY, M. L. STONE, R. E. HOSBACH, and J. MESTERN. *Pediatrics [Pediatrics]* 24, 378-388, Sept., 1959. 3 figs., 20 refs.

The authors of this paper from New York Medical College and the Flower and Fifth Avenue Hospitals, New York, report a study of the activity of the enzymes glutamic oxalacetic transaminase (G.O.T.) and lactic dehydrogenase (L.D.H.) in the serum and cerebrospinal fluid (C.S.F.) of 54 healthy newborn infants, aged 2½ hours to 10 days, and 20 newborn infants, aged 2 to 115 hours, with suspected intracranial birth injury. In the normal infants the plasma G.O.T. activity ranged from 5 to 102 units per ml. per minute (average 36.9 ± 18.9) and the plasma L.D.H. ranged from 440 to 2,540 units per ml. per minute (average $1,165 \pm 543$); the values for the C.S.F. were: G.O.T. 1 to 10 units per ml. per minute (average 4.5 ± 2.2) and L.D.H. 3.3 to 120 units per ml. per minute (average 32.3 ± 24). In the infants with intracranial injury the G.O.T. activity of the C.S.F. showed an increase of 82% over that of normal infants and the plasma G.O.T. an increase of 18%. The L.D.H. activity of the C.S.F. showed a mean increase of 309% over the normal, but the plasma L.D.H. showed an increase of only 11% over normal. It is suggested that the activity of these enzymes in the cerebrospinal

fluid may be helpful in the study of infants in whom intracranial birth injury is suspected.

Winston Turner

1019. Diabetes Mellitus or the Prediabetic State in the Mother and the Neonate. Effect on the Homeostasis of Calcium, Phosphorus, and Some Other Electrolytes in the Neonate on the First Day of Life

I. F. GITTLEMAN, J. B. PINCUS, E. SCHMERTZLER, and F. ANNECCHIARICO. *A.M.A. Journal of Diseases of Children [A.M.A. J. Dis. Child.]* 98, 342-349, Sept., 1959. 18 refs.

In this paper from the Jewish Hospital of Brooklyn, New York, a study is reported of the serum concentration of calcium and of certain other electrolytes during the first day of life in 22 infants born to diabetic mothers and 36 infants born to mothers who were in the prediabetic state—that is, mothers showing a diabetic-like glucose tolerance curve in one or more pregnancies. Full details are given of the clinical findings and the results of the biochemical analyses. Hypocalcaemia was present in both groups of infants. Irritability and oedema were not clearly related to the serum calcium level, but respiratory distress was always associated with a serum calcium level of 8 mg. per 100 ml. or less.

F. P. Hudson

CLINICAL PAEDIATRICS

1020. Effect of Dietary Supplement of Nonfat Milk on Human Growth Failure: Comparative Response in Undernourished Children and in Undernourished Adolescents

T. D. SPIES, S. DREIZEN, R. M. SNODGRASSE, C. M. ARNETT, and H. WEBB-PEPLOE. *A.M.A. Journal of Diseases of Children [A.M.A. J. Dis. Child.]* 98, 187-197, Aug., 1959. 6 figs., 10 refs.

The broad relationship between growth and nutrition is now well established. This paper from the Jefferson-Hillman Hospital (Northwestern University), Birmingham, Alabama, reports a study of the effect of a daily supplement of fat-free milk on children with retarded physical development associated with undernutrition. A sample of 10 boys and 10 girls who were found to be of retarded skeletal and developmental age, as ascertained by radiography of the hand bones and the use of the Wetzel grid, were carefully chosen from amongst patients attending a nutrition clinic. All had a history of undernutrition. Ten ranged in age from 4½ to 12½ years and 10 from 15½ to 16½. After 6 months' initial study they were given a daily supplement of 6 ounces (170 g.) of dried "non-fat" milk for 6 days a week for 6 months, being then kept under observation for a further 6 months. Growth progress was assessed by plotting height, weight, and chronological age on the Wetzel grid and by radiography of the hand and wrist at 3-monthly intervals, and the mean monthly gains in skeletal and developmental age in the two groups during each 6-month period calculated.

In the preadolescent group there was a statistically significant increase in the rate of both skeletal and

developmental growth during the second period, but these increased rates were not maintained when the supplement was stopped and in fact returned to the pre-supplementary level. In the adolescent group there was also a statistically significant acceleration of general body growth during the second period, but not of skeletal maturation, indicating that with increasing age children become less susceptible to the influences which disrupt skeletal maturation, but are still susceptible to those which affect dimensional growth. The increase in growth rates during the supplementary period in the preadolescent group was not sufficient to remove the entire "growth debt", this failure being ascribed to uncorrected deficiencies of such growth factors as iron and vitamins A and C. Marked individual variations in degree of somatic and skeletal growth were observed and were regarded as an indication of individual differences in utilization of the food supplement. Concurrently with this study the biological value of the milk supplement was studied in 5 groups of 30 rats, each receiving different types of basic diet. Some fine colour photographs illustrate the differences in the eyes, general appearance, and mandibles of rats receiving basic diets alone and of those receiving the milk supplement in addition.

David Morris

1021. Comparative Hematologic Response to Iron Fortification of a Milk Formula for Infants

A. MARSH, H. LONG, and E. STIERWALT. *Pediatrics* [Pediatrics] 24, 404-412, Sept., 1959. 6 figs., 18 refs.

Iron-deficiency anaemia is common in infants, especially in those born prematurely. Opinions differ on the degree of absorption of iron when it is given with milk, some evidence suggesting that iron combines with phosphates in milk and absorption is thereby hindered. At the University of Kansas Medical Center, Kansas City, an investigation was carried out designed to determine the value of iron given with the infant's milk during the first 9 months of life.

Healthy full-term and premature infants were studied from birth for 9 months, being divided into 3 groups, each group having a different feeding regimen. Group 1 were given a milk formula to which ferrous sulphate had been added to give 12 mg. of iron in each 32 oz. (908 ml.) of prepared feed; Group 2 received similar milk but without the added iron; and Group 3 received evaporated milk without added iron. All 3 groups were given adequate vitamins. The only solid food allowed was a cereal containing 0.1 mg. of iron per 100 g. If a mother did not adhere to the feeding instructions the infant was dropped from the study. All infants were seen frequently in the first 9 months of life, when a detailed history was taken, the infant was examined, and the haemoglobin, haematocrit, leucocyte count, and serum iron level were determined.

Extra iron was given to an infant in whom the serum iron level fell below 50 μ g. per 100 ml. or the haemoglobin level below 8 g. per 100 ml., this addition being required in 2 full-term infants out of 44 and in 16 premature infants out of 26 in groups 2 and 3. None of the 30 full-term or 16 premature infants in Group 1 became

anaemic. Those requiring treatment were merely changed to the Group-1 regimen with satisfactory results. Apart from the development of anaemia, the infants in Groups 2 and 3 had lower average values for haemoglobin, haematocrit, and serum iron concentration after the age of 3 to 3½ months than the infants in Group 1, these differences continuing to be significant for the 9-month observation period.

The authors conclude that the addition of iron to the infant's milk is advantageous.

F. P. Hudson

1022. Electrocardiographic Changes in Idiopathic Hypercalcaemia of Infancy

E. N. COLEMAN. *British Medical Journal* [Brit. med. J.] 2, 467-470, Sept. 19, 1959. 5 figs., 19 refs.

The electrocardiographic (ECG) changes occurring in 24 children aged from one to 23 months suffering from idiopathic hypercalcaemia have been studied at the Royal Hospital for Sick Children, Glasgow. The highest recorded serum calcium levels ranged from 12 to 18.6 mg. per 100 ml., although it was not always possible to record the ECG when the calcium level was at its highest.

The usual three standard leads were used and recordings were repeated in all abnormal cases; altogether 53 ECGs of adequate quality for critical scrutiny were obtained. ECG abnormalities occurred at some time in 14 of the 24 patients and consisted in S-T elevation, a broad, prominent T wave which was sometimes notched, and prolongation of the corrected Q-T interval. Although in general these changes were correlated with the height of the serum calcium level, in 15 records this relationship broke down completely. There was also no correlation between the serum calcium level and the duration of the cardiac cycle, P-R interval, or QRS complex.

The author reviews the literature relating degree of hypercalcaemia and vitamin D intake to the ECG findings and concludes that the ECG changes observed in the present study were not due directly to the increased serum calcium concentration. Since, however, they did resemble the ECG changes seen in some patients with vitamin-D poisoning, he suggests that they might have been due to an excessive intake of this vitamin, possibly with coronary artery calcification due to the hypercalcaemia.

Gerald Sandler

1023. Giardiasis, a Cause of Celiac Syndrome

J. A. CORTNER. *A.M.A. Journal of Diseases of Children* [A.M.A. J. Dis. Child.] 98, 311-316, Sept., 1959. 1 fig., 23 refs.

The author reports the cases of 4 children with the coeliac syndrome in whom infestation by *Giardia lamblia* was diagnosed by the finding of cysts in the stool. There was a prompt clinical improvement in all the children when they were given mepacrine, 50 mg. 2 or 3 times a day, for 5 days.

A good review and discussion of the literature is included in the paper. The importance is emphasized of not relying on stool examinations for diagnosis and of examining duodenal juice instead when the disease is suspected. The author suggests that although some

children are asymptomatic carriers of *Giardia*, others may develop the coeliac syndrome as a result of interference with absorption from the duodenum and upper jejunum, while others again may have abdominal pain, anorexia, nausea, vomiting, malaise, melaena, gall-bladder colic, jaundice, malnutrition, or diarrhoea.

R. S. Illingworth

1024. Effects of Early Ambulation on the Course of Nephritis in Children

W. W. McCrory, D. S. Fleisher, and W. B. Sohn. *Pediatrics [Pediatrics]* 24, 395-399, Sept., 1959. 1 fig., 8 refs.

The effect of early ambulation on the course of nephritis in children was studied in 35 patients at the Children's Hospital of Philadelphia. The patients, 8 girls and 27 boys aged 2½ to 13 years on admission, were kept in bed during the acute stage of nephritis, but as soon as the acute symptoms had subsided they were allowed gradually to resume full physical activity. All were engaged in normal activity, including attendance at school, within 2 months of the onset of acute nephritis. Penicillin was given in therapeutic doses for the first 7 to 10 days after nephritis was diagnosed and then prophylactically until the Addis count of the urinary sediment was normal. More than half the patients had oedema and hypertension with some increase in the serum non-protein nitrogen level. There was an exacerbation of signs of nephritis with return of gross haematuria after ambulation in only one of the patients, and this was associated with an upper respiratory-tract infection. Most patients had some degree of proteinuria and haematuria at the time of resumption of full activity, but 9 months after the onset of nephritis the erythrocyte sedimentation rate and the results of urine analysis were normal. The Addis count was normal one year after the onset of nephritis in 29 patients; 2 years after the onset the count was normal in all except one. Although the number of patients was admittedly small and there were no controls, the results do not lend support to the view that early ambulation in these cases is associated with unfavourable sequelae.

C. Bruce Perry

1025. Infectious Neuronitis (Guillain-Barré Syndrome) in Children

A. F. Peterman, D. D. Daly, F. R. Dion, and H. M. Keith. *Neurology [Neurology (Minneapolis)]* 9, 533-539, Aug., 1959. 3 figs., 10 refs.

Data have been reported concerning clinical observations, laboratory examinations, and course of illness in 26 cases of infectious neuronitis developing in children less than 16 years of age. In approximately two-thirds of the cases, the disease occurred before the age of 8 years, although ages ranged from 16 months through 15 years. The ratio of males to females was greater than 2·7 to 1. Antecedent infection had occurred in 18 patients, although in some this may have been coincidental.

Progressive symmetric muscular weakness was the chief complaint. Involvement of muscles of the limbs occurred most often; however, in almost half the

patients, weakness developed in muscles supplied by cranial nerves. Areflexia was present in all patients at some time in the illness. Although sensory disturbances were not common, impairment in perception of vibration and proprioception was found in 7 patients. Examination of the cerebrospinal fluid in 25 cases revealed albuminocytologic dissociation in all but one case, the protein attaining its highest level 10 to 25 days after appearance of clinical symptoms. Electromyographic examinations revealed features compatible with involvement of lower motor neurons of peripheral nerves in the 10 patients so examined. Reduction in conduction velocity of peripheral nerves was a frequent observation, particularly after the first month of illness.

The course of the disease was prolonged in 11 of the 17 patients who nevertheless recovered completely from 6 months to 3 years later. Two of these patients had relapses. Seven had persistent weakness and atrophy of distal muscles of the legs 3 to 5 years after onset of their disease. One died of pneumonia secondary to weakness of the muscles of respiration. One was lost to follow-up study.

Problems in differential diagnosis are important as neuronitis may be confused with poliomyelitis, muscular dystrophy, or polymyositis.—[Authors' summary.]

1026. Treatment of Hypsarrhythmia with ACTH

F. W. Stamps, E. L. Gibbs, I. M. Rosenthal, and F. A. Gibbs. *Journal of the American Medical Association [J. Amer. med. Ass.]* 171, 408-411, Sept. 26, 1959. 3 figs., 14 refs.

This paper from the University of Illinois College of Medicine, Chicago, reports 60 cases of hypsarrhythmia treated with corticotrophin. Hypsarrhythmia is defined as a distinctive electroencephalographic (EEG) pattern associated clinically with epileptic-like spasms in infants, this pattern consisting in high wave-and-spike discharges of very high voltage which vary in both duration and location from moment to moment. The spasms are characterized by jerking or flexion of the body, with rolling upwards of the eyes and flinging out of the arms, and are usually short-lived although of somewhat longer duration than myoclonic seizures. Some of the patients have grand mal attacks. Hypsarrhythmia usually develops between the 3rd and 12th months of life, but in the present series the patients' ages ranged from one day to 3 years. Before ACTH was available the disease carried a poor prognosis, 11% of patients dying before their 3rd year and 87% of the survivors being feeble-minded.

The present series of patients were treated with ACTH, infants being given 5 units of the hormone by intramuscular injection daily for 5 days, this dose being increased by 5 units every 5th day until the 15th day, when the EEG was again recorded and compared with the pre-treatment record. If there was no evidence of improvement in the EEG the dosage was gradually increased up to a maximum of 50 units per day and treatment continued, in a few cases for 120 days. The EEG returned to normal in 5 cases and showed a considerable improvement in a further 31. Of the 5 patients in the former group, 3 became clinically normal and 2 were much

improved. Of the other 31 patients, 13 (42%) became free from seizures and in 12 (40%) their number was much reduced; 6 did not respond. Clinically, 3 (10%) became normal and 15 (50%) were greatly improved, although 9 (30%) subsequently relapsed.

The aetiology of the hypsarrhythmia was variable; in 28 of the 60 cases there was no history of other illness before the onset, but in the other cases the onset was variously associated with encephalitis, infectious diseases of childhood, triple-vaccine inoculation, meningitis, otitis, and mongolism. There was no correlation between the aetiology and the response to ACTH treatment, and no relationship could be established between the therapeutic effect of ACTH and the concomitant use of tranquillizing or anticonvulsant drugs. The authors conclude that the response to ACTH in this serious disease is variable for reasons not yet understood and that at the present time it cannot be predicted which cases of hypsarrhythmia will respond and which will not.

J. B. Stanton

1027. **Flexion-spasm Disease.** (La malattia degli spasmi in flessione)

G. B. CAVAZZUTI. *Lattante* [Lattante] 30, 441-456, Aug., 1959. 6 figs., 18 refs.

The author opens with a brief summary of recent work on flexion spasm and then describes the results obtained in 15 children treated with anticonvulsant drugs such as "mysoline" (primidone), "dintoina", or "luminal" (phenobarbitone) together with ACTH (corticotrophin) at the Paediatric Clinic of the University of Modena. Of the patients, 11 were found to derive little permanent benefit. Some were unaffected by the treatment, while others showed varying diminution in the length and severity of the attacks. However, the remaining 4 children appeared to be cured, 3 of these having been treated with anticonvulsants and the fourth with prednisone. The author points out that the delay in psychomotor development remains long after the spasms have ceased; thus in one of the present patients it was 2 years before a normal level of development was reached. He was unable to find any common origin for the attacks. There was some indication that the prognosis was best in those patients in whom the response to therapy was both early and well marked.

J. G. Jamieson

1028. **Flexion Spasms and Their Treatment with ACTH and Hydrocortisone.** (Über die Blitz-Nick-Salaam-Krämpfe und ihre Behandlung mit ACTH und Hydrocortison)

G. DUMERMUTH. *Helvetica paediatrica acta* [Helv. paediat. Acta] 14, 250-270, Sept., 1959. 4 figs., 20 refs.

From the University Paediatric Clinic, Zürich, the author reports that as the result of treating 10 children, all but one under 3 years of age, suffering from typical attacks of flexion spasm with ACTH or hydrocortisone 6 were definitely benefited by the treatment, but the other 4 showed no improvement, nor did 2 atypical cases of the disorder. Neither the history nor the clinical and laboratory findings pointed to any obvious cause for the difference in results. The cases are described in detail.

In the children who improved the encephalogram (EEG) became more nearly normal, they became quieter, showed more coordination in their movements, and in one case particularly the retardation in development became less marked. A follow-up report states that after 3 months' intermittent therapy one child had become free of attacks, though a skull injury had caused a temporary relapse, while a second case after 4 months' therapy showed both clinical improvement and the absence of signs of epileptic activity in the EEG. Side-effects were not serious; most of the children developed a plethoric appearance of the face and a much larger appetite, and 2 developed a temperature which could not be attributed to infection.

When ACTH was given as a first treatment all other anticonvulsant drugs were withheld so that the effect of ACTH alone could be assessed; however, when improvement set in an anticonvulsant was also prescribed. Intermittent therapy is considered essential, since relapses do occur, and also the long continued administration of large doses of cortisone may provoke grand mal seizures.

J. G. Jamieson

1029. **Structural Alterations in the Cerebellum in Cases of Cerebral Palsy. Their Relation to Residual Symptomatology in the Ataxic-Atonic Group**

C. B. COURVILLE. *Bulletin of the Los Angeles Neurological Society* [Bull. Los Angeles neurol. Soc.] 24, 148-165, Sept., 1959. 2 figs., 25 refs.

At the Cajal Laboratory of Neuropathology, Los Angeles County Hospital, the author has investigated post mortem the incidence of cerebellar lesions (and the relationship of such lesions to symptoms) in cases of cerebral palsy. Of 126 such patients who had survived for at least one year cerebellar lesions were found in 8, of which 5 are described in some detail. The typical picture was of a cerebellum which appeared normal macroscopically, but on section showed diffuse cortical atrophy, with selective loss of Purkinje and granule cells, later followed by degeneration of corticofugal nerve fibres and by gliosis. In cases in which gross cerebellar lesions such as generalized atrophy and diffuse cortical sclerosis were present the cerebrum was similarly affected. In no case was cerebellar damage alone found, all showing also major lesions in the cerebrum. Only one patient, a child aged 16 months, presented with pure cerebellar symptoms, manifested by generalized atonia. In all the other patients any cerebellar symptoms were overshadowed by the motor and mental manifestations of the cerebral lesions.

The author points out that the widespread and uniform nature of the cerebellar lesions indicates an anoxic origin, although embryological, traumatic, and inflammatory causes are other aetiological possibilities. He suggests that closer study be made of cerebellar lesions in cases of cerebral palsy, and if ataxic-diplegic cases were differentiated from atonic-ataxic cases at clinics the disappointing response to treatment in the latter would be better understood; by the nature of their predominating cerebellar lesions these patients are very resistant to the usual measures of physical therapy directed towards their rehabilitation.

Janet Q. Ballantine

Medical Genetics

1030. Evidence for the Existence of the Human "Super Female"

P. A. JACOBS, A. G. BAIKIE, W. M. COURT BROWN, T. N. MACGREGOR, N. MACLEAN, and D. G. HARNDEN. *Lancet [Lancet]* 2, 423-425, Sept. 26, 1959. 4 figs., 10 refs.

A case is described from the Western General Hospital, Edinburgh, in which a chromosome anomaly characterized by a chromosomal number of 47 and a chromosomal sex of type XXX was found in a female patient first seen in 1946 because of amenorrhoea. This anomaly is considered to be analogous to the "super female" observed in *Drosophila melanogaster*. It is suggested that in man this condition may affect only the genital tract.

G. Calcutt

1031. Chromosome Studies in Human Leukaemia

A. G. BAIKIE, W. M. COURT BROWN, P. A. JACOBS, and J. S. MILNE. *Lancet [Lancet]* 2, 425-428, Sept. 26, 1959. 1 fig., 12 refs.

The occurrence in neoplastic cells of chromosomal abnormalities, both of number and form, is now well established. In this paper from the Western General Hospital, Edinburgh, a case of acute leukaemia in a woman aged 56 is described in which a modal chromosome number of 48 and other chromosome abnormalities occurred. These abnormalities persisted for 7 months during treatment with steroids. Thereafter, shortly before the patient's death, the modal chromosome number changed to 47.

Examination of the bone-marrow chromosomes in 10 further cases of leukaemia and 2 of myelomatosis showed that of 4 cases of acute leukaemia, one showed an abnormality of chromosome number and 2 morphological abnormalities. In contrast, no chromosomal abnormalities were found in 6 cases of chronic leukaemia or in the 2 cases of myelomatosis.

G. Calcutt

1032. On the Inheritance of the Haptoglobin Serum Groups. [In English]

O. MÄKELÄ, A. W. ERIKSSON, and R. LEHTOVAARA. *Acta genetica et statistica medica [Acta genet. (Basel)]* 9, 149-166, 1959. 15 refs.

Evidence has recently been published which supports the theory that the haptoglobin serum groups are determined by two autosomal genes with incomplete dominance. It has been proposed that the genes should be described as Hp^1 and Hp^2 and the resultant three phenotypes as $Hp\ 1-1$, $Hp\ 2-1$, and $Hp\ 2-2$. Generally no haemoglobin-binding protein can be demonstrated in children under about 4 months of age, the Hp type in such instances being described as "undeveloped". In an extensive study of family material, Harris *et al.* (*Nature (Lond.)*, 1958, 182, 1324) found four instances of incompatible homozygosity between mother and child,

all of which occurred in closely related persons; the incompatibility was attributed to a so-called "silent" gene in the family. This paper from the University of Helsinki presents data derived from a study of the haptoglobin groups in Finnish subjects which are used to test the validity of the earlier results. The technique of determining the Hp -types of the members of the population groups examined was essentially that used by earlier workers. Four groups of persons were studied: (1) 891 healthy and unrelated adults; (2) 126 families consisting of parents and at least one child—in all there were 419 children; (3) 222 combinations of mother and child, not included in the previous families; and (4) 263 pairs of twins drawn from a series of male twins born between 1920 and 1929.

The distribution of the 891 unrelated adults according to their Hp type appeared to be independent of sex and ABO, MN, and Rh blood-group distributions. Two of the 891 were of the "undeveloped" type; of the remainder, 14.5% were $Hp\ 1-1$, 42.1% were $Hp\ 2-2$, and 43.4% were $Hp\ 2-1$. The gene frequencies were deduced as 0.362 for Hp^1 and 0.638 for Hp^2 .

The material relating to the 126 families included 35 matings in which each partner was homozygous. This group consisted of one mating $Hp\ 1-1 \times Hp\ 1-1$ yielding one child of Type $Hp\ 1-1$, 12 matings $Hp\ 1-1 \times Hp\ 2-2$ yielding 43 children of Type $Hp\ 2-1$, and 22 matings $Hp\ 2-2 \times Hp\ 2-2$ yielding 92 children of Type $Hp\ 2-2$. Among 69 matings in which one partner was homozygous and one heterozygous there were 24 matings $Hp\ 1-1 \times Hp\ 2-1$ yielding 38 children of Type $Hp\ 2-1$ and 32 of Type $Hp\ 2-1$ and 45 matings $Hp\ 2-2 \times Hp\ 2-1$ yielding 78 children of Type $Hp\ 2-1$ and 70 of Type $Hp\ 2-2$. Finally there were 22 matings in which both partners were heterozygous ($Hp\ 2-1 \times Hp\ 2-1$), which yielded 18 children of Type $Hp\ 1-1$, 36 of Type $Hp\ 2-1$ and 11 of Type $Hp\ 2-2$. It is clear that in these data there were no instances of homozygosity incompatible with the homozygous parent. There was no material difference between these observed distributions of offspring and those expected theoretically on the hypothesis under test. The full details of these families are set out in an appendix.

The material relating to the 222 mother-and-child combinations included 119 homozygous mothers; 27 of these were of Type $Hp\ 1-1$, and they had 8 children of the same type and 19 of Type $Hp\ 2-1$; 92 were of Type $Hp\ 2-2$, and they had 57 children of the same type and 35 of Type $Hp\ 2-1$. Thus again no instance of incompatibility between homozygosity of parent and child was encountered and theoretical expectations were well matched by observation. The remaining 103 mothers of Type $Hp\ 2-1$ had 17 children of Type $Hp\ 1-1$, 37 of Type $Hp\ 2-2$, and 48 of Type $Hp\ 2-1$.

Of the 263 pairs of twins, 61 were considered to be monozygotic for reasons which are given, and within each such pair the Hp types were identical. Of the 202

twin pairs considered to be dizygotic, different Hp types were found in the two members of 69 pairs and identical Hp types in those of 133 pairs.

The extensive data reported in this paper support the theory of inheritance by two autosomal genes with incomplete dominance, and from the data relating to the mother-and-child combinations the authors estimate the maximum gene frequency of the "silent" gene (H_p^0) as 0.02. However, this is not to say that H_p^0 does, in fact, exist in the population group studied. A slight, though not significant, excess of homozygotes (503 compared with 478 expected) in the data relating to the 891 unrelated adults might be explained by the existence of such an allele.

E. A. Cheeseman

1033. Cytogenetical Observations in Mongolism. [In English]

J. A. BÖÖK, M. FRACCARO, and J. LINDSTEN. *Acta paediatrica [Acta paediat. (Uppsala)]* 48, 453-468, Sept., 1959. 10 figs., 30 refs.

After a review of current work on chromosomal variations in man observations on 3 patients with mongolism are described. Chromosome studies by the cell culture technique using cells from bone marrow and skin showed a modal number of 47. This confirms quite recent results reported by French and British workers. The type of the 47th chromosome is discussed briefly.—[Authors' summary.]

1034. Genes on the Y Chromosome Influencing Rate of Maturation in Man: Skeletal Age Studies in Children with Klinefelter's (XXY) and Turner's (XO) Syndromes

J. M. TANNER, A. PRADER, H. HABICH, and M. A. FERGUSON-SMITH. *Lancet [Lancet]* 2, 141-144, Aug. 22, 1959. 19 refs.

In this joint study reported from the Universities of London, Glasgow, and Zürich the authors have determined the height, weight, and skeletal age of 27 individuals aged between 6 and 18 years with Klinefelter's syndrome, of whom 19 were from Zürich and 8 from Glasgow, all being mentally retarded. Similar data were also obtained for 17 children with Turner's syndrome, of whom 9 were from Zürich and 8 from London.

It was found that the skeletal age of the patients with Klinefelter's syndrome, who have the genotype XXY, was very similar to control male children (genotype XY); while the patients with Turner's syndrome, who have the genotype XO, had a skeletal age very similar to that of control female children (genotype XX). The height of the children with Klinefelter's syndrome from Zürich was above that of control males, but this was not the case with the patients from Glasgow, the explanation of the difference probably being that the latter group included more patients with severe mental retardation. Children with Klinefelter's syndrome had relatively long legs at all ages and a somewhat feminine or eunuchoid body build. The height of the patients with Turner's syndrome was much less than that of control females; the body build of these subjects has not been fully studied. The authors suggest that their findings indicate that the genes on the Y chromosome are the cause of the normal

sex dimorphism in the rate of development, as measured by skeletal age, in man and the primates. This is probably a direct effect rather than due to the action of androgens produced by the testis, since androgens appear to cause an advance and not a delay in maturation. In contrast, masculine body build is not due to genes on the Y chromosome, since it is absent in children with Klinefelter's syndrome. This suggests that a "double dose" of X inhibits the development of a masculine body build.

C. O. Carter

1035. Studies on the Genetic Mechanism of Cystic Fibrosis of the Pancreas

M. SMOLLER and D. YI-YUNG HSIA. *A.M.A. Journal of Diseases of Children [A.M.A. J. Dis. Child.]* 98, 277-292, Sept., 1959. 6 figs., 21 refs.

At the Children's Memorial Hospital, Chicago, the authors have studied the sodium and chloride concentrations in the sweat of the members of 38 families in which one or more children had fibrocystic disease of the pancreas and in a group of healthy individuals as controls. On the hypothesis that the illness is due to a recessive gene it would be expected that all the parents and two-thirds of the siblings of affected children would be heterozygous carriers of the gene.

The controls were clearly distinguished from the affected children by the sodium and chloride concentrations in the sweat. In the heterozygous parents the range of these concentrations overlapped that in both the control group and the affected children. The brothers and sisters of the patients also showed overlap with both these groups, the mean concentration values being compatible with the assumption that two-thirds were heterozygotes like the parents and one-third homozygous normal individuals like the controls. About half the heterozygotes for the gene in question showed sweat sodium and chloride concentrations outside the range of those in the controls. No similar evidence of heterozygote manifestation, however, was provided by estimations of trypsin activity in the stools or from studies of inflammation of the lung. The detailed results of the sweat sodium and chloride estimations, stool trypsin content, and respiratory status of the members of the 38 families are tabulated.

Comparison of the manifestations of the illness as they appeared in affected members of the same family showed some similarity within families in respect of deficiency of duodenal enzymes, the degree of pulmonary involvement, and the sodium and chloride concentrations in the sweat; but the authors point out that a larger study is needed to confirm this and that there is no need at the moment to suppose that more than one gene may be involved in the causation of fibrocystic disease of the pancreas since, as has been shown in other conditions, such a single gene could be modified by other genes or by certain environmental factors to produce the variable clinical picture seen.

C. O. Carter

1036. Quantitative Genetics of Palmar Dermatoglyphics

J. PONS. *American Journal of Human Genetics [Amer. J. hum. Genet.]* 11, 252-256, Sept., 1959. 2 figs., 4 refs.

Public Health and Industrial Medicine

PUBLIC HEALTH

1037. The Prognosis for the Foetus of Mothers of Forty Years of Age and Over

J. RENDLE-SHORT. *Journal of Obstetrics and Gynaecology of the British Empire* [J. Obstet. Gynaec. Brit. Emp.] 66, 657-659, Aug. [received Oct.], 1959. 3 refs.

The case records of infants born at the Jessop Hospital for Women, Sheffield, to mothers 40 years old or over during the years 1952-6 inclusive were studied. The follow-up period varied from 10 days to one year. Of the 255 liveborn babies of such mothers, 7 died, giving a death rate of 27.4 per 1,000, whereas of the 8,033 children of mothers below 40, 185 died, giving a death rate of 23.1 per 1,000. One of 2 children born to mothers aged 48 years was healthy and normal. The stillbirth rate for mothers of 40 or more was 59.0 per 1,000 births as against 40.8 per 1,000 births for mothers under 40.

Although congenital abnormalities occurred in a number of the babies born to older mothers, the numbers were too small for definite conclusions to be drawn. The incidence of mongolism was 11.4 per 1,000 live births, which is fairly close to the figure of 14.8 per 1,000 found in a much larger series of children of mothers over 40 years old reported by Carter and MacCarthy (*Brit. J. soc. Med.*, 1951, 5, 183; *Abstr. Wld Med.*, 1951, 10, 375). One happy, though tentative, conclusion reached by the author is that the bad prognosis for live birth often given to the "elderly primipara" is not quite justified by the figures in this series, 73 out of 75 primiparae over the age of 40 bearing a live child.

J. Browne Kutschbach

1038. Social and Biological Factors in Infant Mortality. Variation of Mortality with Mother's Age and Parity

J. A. HEADY and J. N. MORRIS. *Journal of Obstetrics and Gynaecology of the British Empire* [J. Obstet. Gynaec. Brit. Emp.] 66, 577-593, Aug. [received Oct.], 1959. 7 figs., 30 refs.

The data studied in this paper from the Social Medicine Research Unit of the Medical Research Council, London Hospital, in which the relation of maternal age and parity to the stillbirth rate and infant mortality is discussed, relate to the 1,351,106 single legitimate births (including stillbirths) in England and Wales in 1949 and 1950 and to the deaths during the first year of life of babies born during this period. The stillbirth rate rose with the mother's age from 16 per 1,000 at 20 to 24 years to 47 per 1,000 at 40 to 44 years. The stillbirth rate was high among "elderly primiparae" and older mothers of large families. Post-neonatal mortality (that is, between 4 weeks and one year) increased with the birth rank of the child and the size of the family. It was high among the children of young mothers with large families.

Neonatal mortality (0 to 4 weeks) was lowest for first-born babies of mothers aged 30 to 34 and was high for "elderly primiparae" and "grand multiparae" (where the child was 6th to 10th in birth rank). In addition, as with post-neonatal mortality, neonatal mortality was high among the babies of young multiparae. The average neonatal mortality rate was 16 per 1,000, the lowest rate, 11 per 1,000, being found in the second-born children of mothers aged 25 to 29. The high mortality rate in the first week of life among the children of young multiparae was in contrast to their low stillbirth rate. These variations in infant mortality with maternal age could not be accounted for by the social class distribution of births to mothers of different ages, though a "social" cause of the variation could not be excluded. Since young multiparae have a high prematurity rate and their babies a high mortality in the neonatal and post-neonatal periods, these mothers and children must be regarded as a "vulnerable" group which should receive special care.

J. Browne Kutschbach

1039. Pathological Reports for Mortality Statistics

C. L. ERHARDT, L. WEINER, and G. McAVOY. *Journal of the American Medical Association* [J. Amer. med. Ass.] 171, 33-36, Sept. 5, 1959. 9 refs.

Since 1945 it has been required in New York City that pathologists should report the results of necropsies to the vital statistics office in order that the cause of death as originally reported on the death certificate could be revised if necessary. This requirement was at first only partially observed, but after a reminder had been sent to the hospitals concerned the number of returns received in 1956 was almost double that in 1955, totalling 5,217, and the present report is based on a study of these reports. In only 794 cases (15.2%) was it necessary to change the stated cause of death, and in many instances the new diagnosis was within the same cause group. The maximum net change in the number of deaths from any one cause (as listed in the *International List of Causes of Death*) was +2.1%, with the exception of causes specific to infants, where the number of deaths due to infections of the newborn was increased by 9.9%. To determine the effect of supplementary necropsy reports on vital statistics the authors studied the 30,634 cases of death from arteriosclerotic and degenerative heart disease notified during the year and found that after allowing for transfers within the group there were only 118 removals and 62 additions as a result of necropsy reports, making a net change of -56 (-0.2%) only. Similarly, the final total of 16,896 deaths from malignant neoplasms represented a net change of +72 (+0.4%) only from the previous total. This experience in New York City (where, it should be noted, 68% of all deaths occur in hospitals) has led the Board of Health to limit the requirement for necropsy reports to deaths in infants.

F. T. H. Wood

1040. Psychosomatic Problems in a Rapidly Growing Suburb

R. E. GORDON and K. K. GORDON. *Journal of the American Medical Association [J. Amer. med. Ass.]* 170, 1757-1764, Aug. 8, 1959. 13 refs.

In this paper from Columbia University, New York, and Englewood Hospital, New Jersey, the authors describe an investigation of the hypothesis that differences in the incidence of psychosomatic disorders are related to differences in the way of life in different communities. They chose asthma as a representative psychosomatic disorder, coronary thrombosis, duodenal ulcer, and essential hypertension as representing "tension disorders", and bronchopneumonia as a control non-psychosomatic disease. They then compared the admissions for these diseases, expressed as the percentages of total medical admissions, during 1957 in three hospitals each serving a different type of area near New York: (1) a rapidly increasing suburb; (2) a moderately increasing mixed rural community; and (3) a stable rural area. The incidence of bronchopneumonia was similar in all three areas, that of asthma was significantly greater than the average in Area 2, and that of each of the other conditions was significantly greater in Area 1.

The authors conclude from these findings that the greater incidence in the rapidly increasing suburb of disorders which they regard as resulting from tension is the result of specific stresses involved in the way of life in this area. They discuss possible sources of stress in such communities, mentioning upward striving, cut-throat competition, and the need for "conspicuous consumption". They consider that the struggle of married women to cope with these stresses explains an increase which they had observed in the incidence of "tension disorders" between 1950 and 1958 in the rapidly increasing suburb.

[Throughout this study the authors assume that the patients admitted to hospital are typical in their social characteristics of the community from which they come. They do not consider any of the other possible explanations of their findings.]

Christopher Wardle

1041. The Disinfection of Bath Water with Hexachlorophane

G. A. J. AYLIFFE, V. G. ALDER, and W. A. GILLESPIE. *Lancet [Lancet]* 2, 456-458, Sept. 26, 1959. 3 figs., 5 refs.

In the course of a study at the Royal Infirmary, Bristol, of cross-infection in surgical wards methods of disinfecting baths were examined.

Laboratory experiments showed that four strains of *Staphylococcus aureus* with different phage patterns and many other bacteria were killed by hexachlorophane in the concentration used in bath water. Gram-negative bacilli were found to vary in sensitivity, but were less sensitive than staphylococci. A stock 10% (w/v) solution was made by dissolving 100 g. of hexachlorophane in 400 ml. of industrial spirit and 10 g. of sodium hydroxide in 500 ml. water, mixing the two solutions and making the volume up to one litre with water; 1 oz. (28 ml.) of this solution was added to each bath.

2A

The viable bacterial counts of the bath water of healthy adult volunteers rose from less than 200 per ml. before the subject entered the water to several thousand per millilitre within a few minutes of entry; with the addition of hexachlorophane to the bath water there was a rapid fall in the count to approximately initial levels. The bacterial counts of bath water of male surgical patients were considerably lowered by the addition of hexachlorophane. High counts were occasionally seen, in spite of the use of hexachlorophane, when patients with open wounds took baths. Conversely, low counts were sometimes observed when the patient had recently taken several hexachlorophane baths, even when the disinfectant was omitted from subsequent baths, indicating possibly a cumulative effect of the disinfectant on skin bacteria. Swabs rubbed over the sides of emptied baths in two wards where hexachlorophane was used gave much lower counts and contained fewer staphylococci than similar swabs from a control ward. Skin sensitization did not occur.

The authors consider that the addition of hexachlorophane to bath water may help to control cross-infection.

H. Caplan

1042. Pertussis Immunization in Pediatric Practice and in Public Health

R. W. PROVENZANO, L. H. WETTERLOW, and J. IPSEN. *New England Journal of Medicine [New Engl. J. Med.]* 261, 473-478, Sept. 3, 1959. 2 figs., 8 refs.

A comparative study is reported of the efficacy of two methods of immunization against whooping-cough. The first method, which had been used in general practice for a number of years by the senior author, consisted in giving the child at the age of 3 to 4 weeks three injections of plain pertussis vaccine (0.5 ml., 1 ml., and 1 ml. respectively) at intervals of 3 weeks, followed 2 to 4 months later by two inoculations each of 0.5 ml. of triple vaccine (diphtheria, pertussis, and tetanus—D.P.T.). The second method, described as the "standard" procedure, consisted in three injections, each of 0.5 ml. of D.P.T., at monthly intervals starting when the child was 3 months old, followed by a booster dose one year later. All the vaccines were routine preparations from the Massachusetts Public Health Biologic Laboratories, Boston; (full details of the antigenic content of the preparations are given).

Serum for antibody titration was taken by heel puncture and an agglutination technique with a suspension of *Bordetella pertussis* suitably standardized in a photometer was used. A reference hyperimmune human serum and a saline control of the antigen were employed in each test. After an adjustment had been made for different intervals between the time of blood sampling and the last inoculation it appeared that in the group receiving 5 injections the antibody titre was twice as high as in the group receiving 3 inoculations. No difference was observed between the groups in the response to the booster dose.

Of 292 children receiving 1,181 injections only 19 showed any marked reactions, none of which was serious in spite of the relatively large amount of pertussis antigen given.

[It should be noted that the Whooping-Cough Immunization Committee of the Medical Research Council [*Brit. med. J.*, 1959, 1, 994; *Abstr. Wld Med.*, 1959, 26, 395] consider that the mouse protection test is a far better measure of the efficacy of a vaccine than agglutinin production.]

A. E. Wright

1043. Diphtheria and Tetanus Toxoids Combined with Pertussis and Poliomyelitis Vaccines: Clinical Trial of a Quadruple Antigen

R. J. WILSON, G. W. O. MOSS, F. C. POTTER, and D. R. E. MACLEOD. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] 81, 450-453, Sept. 15, 1959. 1 fig., 1 ref.

The authors report (from the Connaught Medical Research Laboratories, Toronto), the results of a clinical trial of a formalin-inactivated poliomyelitis vaccine given in a quadruple mixture in combination with the triple diphtheria-pertussis-tetanus toxoid (D.P.T.) vaccine preserved with benzethonium chloride. In this mixture (D.P.T.-polio vaccine) the poliomyelitis vaccine produced slightly higher antibody levels in monkeys than when given alone, and showed no loss of potency after 14 months' storage.

In the clinical trial three doses of this D.P.T.-polio vaccine were given to 33 infants aged between 3 and 4 months and to 18 aged between 5 and 12 months at intervals of 4 weeks. Those under 6 months of age received 0.5 ml. for the first dose and 1 ml. for the other two doses; no undue reactions to this dosage were observed. Approximately 50% of the infants possessed poliovirus antibody of maternal origin before vaccination. After vaccination the median level of poliovirus antibody rose from 1:4 to 1:64 to Type-1 virus, and from 1:4 to 1:128 to Types 2 and 3. All infants without antibody to Types 2 and 3 responded, but one without antibody to Type 1 did not. Although only 8 infants were available as controls, these all responded to all 3 virus types when given the poliomyelitis vaccine alone in a similar dosage. The responses were much better than those seen in a series of 54 infants of similar ages given 2 doses of poliomyelitis vaccine at one month's interval as initial immunization.

The response to the tetanus toxoid was good in all the infants, only 5 (10%) failing to achieve a level of diphtheria antitoxin of 0.01 unit per ml., which is generally accepted as the protective level. At 12 months after the initial course, when a fourth, booster, dose was given, poliovirus antibody titres had then declined to less than 1:4 for Type 1 in 76% of the infants, for Type 2 in 73%, and for Type 3 in 85%. After the booster dose, however, only 15% showed no detectable antibody to Type 1, 4% to Type 2, and 8% to Type 3. All the infants tested had satisfactory titres of diphtheria and tetanus antitoxin. These responses, while considered highly satisfactory, suggest that the first dose of the quadruple D.P.T.-polio vaccine should not be reduced to 0.5 ml. in infants under 6 months of age as was done in this trial, since to do so diminishes the volume of the poliomyelitis vaccine component against Type-1 virus.

A. Ackroyd

1044. Poliovirus Antibody Response after Various Vaccination Schedules and at Different Ages

D. R. E. MACLEOD, C. W. J. ARMSTRONG, G. W. O. MOSS, F. C. POTTER, and R. J. WILSON. *Canadian Medical Association Journal* [*Canad. med. Ass. J.*] 81, 443-449, Sept. 15, 1959. 5 figs., 16 refs.

Further to their previous study of the antibody response to vaccination against poliomyelitis in Canadian school-children (*Canad. J. publ. Hlth*, 1957, 48, 96; *Abstr. Wld Med.*, 1957, 22, 149) the authors now report follow-up observations on the response of 269 of these children (considered in 3 age groups ranging from 6 to 14 years), 54 infants aged 3 to 12 months, and 110 adults aged 21 to 60 years to various schedules of poliomyelitis vaccination.

After 2 doses of vaccine given 4 weeks apart most of the children and adults showed a response, but 9 failed to develop antibody to Type-1 virus and 4 to Type 3 among the 53 initially negative for all 3 types. After 10 months, when the median antibody levels had declined 2- to 4-fold, a booster dose resulted in the development of antibody to all three types in all children, and satisfactory antibody levels were still present in all but a few of 92 children tested 18 months after the booster. In the infants the initial responses were less good than in the school-children, but all except 2 responded to the booster dose with antibody to all 3 types. It is suggested that this difference in response could have been due to persistent maternal antibody, to sensitization of some of the children from previous poliomyelitis infection, and possibly also to some developmental factor. It was noted that 2 doses of vaccine spaced 4 or more weeks apart gave a much better response than a single dose, but the response to a second single dose given 7 or 10 months after the first was as good as when given one month after the first. Also 3 doses of vaccine given within a period of 4 weeks produced no greater response than did 2 doses, but if the 3 were given over a period of 2 months with a month between doses there was a greater response in some cases. The authors recommend that the booster dose should be given not less than 4 weeks after the second dose and before the next poliomyelitis season.

A. Ackroyd

1045. Responses of 6- and 9-Months-old Infants to Two and Three Doses of Poliomyelitis Vaccine

F. T. PERKINS, R. YETTS, and W. GAISFORD. *British Medical Journal* [*Brit. med. J.*] 2, 530-532, Sept. 26, 1959. 1 fig., 7 refs.

In this study, reported from the Biological Standards Control Laboratory, M.R.C. Laboratories, London, of the response of young infants to poliomyelitis vaccine it was shown that in 13 out of 15 infants aged 6 months and in all of 14 aged 9 months the level of placentally transmitted maternal poliovirus antibodies had fallen to non-inhibitory levels by this age. They were then given three 1-ml. doses of poliomyelitis vaccine intramuscularly at monthly intervals, two different commercial vaccines being used, of which the one given to the 6-month-old infants had a slightly higher potency against Type-1 virus. After 2 doses the antibody responses

to polioviruses of Types 2 and 3 were good in all the infants except the 2 who had still inhibitory maternal antibody levels, but there was no response to Type 1 in 3 of the 6-month-old infants and in 6 of those aged 9 months. After the third dose, however, the responses were entirely satisfactory to all 3 types in all the infants (except to Types 2 and 3 in the 2 infants with inhibitory maternal antibody levels), the geometric mean titres increasing about tenfold in both groups. Although all the infants responded with antibodies to Type-1 virus, the geometric mean titre for the 6-month-old infants was more than 12 times that in the older group. This finding emphasizes the importance of using only vaccines highly potent in the Type-1 component and of giving three doses at monthly intervals for the primary immunization of infants of this age. A. Ackroyd

1046. **Asian Influenza in the United States, 1957-1958** Y. TROTTER JR., F. L. DUNN, R. H. DRACHMAN, D. A. HENDERSON, M. PIZZI, and A. D. LANGMUIR. *American Journal of Hygiene* [Amer. J. Hyg.] 70, 34-50, July, 1959. 8 figs., 16 refs.

Epidemiological patterns of the 1957-1958 Asian influenza epidemic in the United States were determined by surveillance techniques. Data were obtained from a nationwide county reporting system, weekly industrial absentee reporting, the National Health Survey, weekly mortality reports, and personal communications from health authorities.

First cases in the United States occurred June 2, 1957, but the epidemic peak was reached in late October. Geographically the epidemic began in southern and coastal states and spread inward toward the central states. Within individual cities students were first affected, followed in about 2 weeks by adults. The peak of deaths usually occurred after the peak of morbidity. There is evidence that this represents later involvement of old and debilitated persons. A second wave of deaths reached its peak in late February, 1958. Although the second wave of deaths almost equalled the first, influenza epidemics had greatly decreased in frequency. Investigations have failed to reveal any single clear-cut cause of this second death wave in the absence of widespread epidemics.—[Authors' summary.]

1047. **Water-borne Infectious Hepatitis.** [Review Article]

J. W. MOSLEY. *New England Journal of Medicine* [New Engl. J. Med.] 261, 703-708, Oct. 1, 1959, and 748-753, Oct. 8, 1959. 2 figs., bibliography.

1048. **An Epidemic of Typhoid Fever Due to the Consumption of Infected Meat Products.** (Über eine Typhus-Epidemie nach dem Genuss von infizierten Fleischwaren) J. KEMNA and V. LENK. *Öffentliche Gesundheitsdienst* [Öff. Gesundh.-Dienst] 21, 240-246, Sept., 1959. 14 refs.

A report is presented on the outbreak of a limited epidemic of typhoid fever in certain suburbs of Berlin affecting 29 persons. The infection originated from a typhoid carrier who lived above a meat shop. Owing to heavy rainfall, defective traps on the waste pipes, and

drains choked with solidified grease a reflux of dirty water occurred leading to an overflow in the lower rooms and kitchen which were used for the manufacture of meat products and sausages. Assay of the Vi antigen revealed that the infection of 20 patients was due to the same source. Franz Heimann

INDUSTRIAL MEDICINE

1049. **Respiratory Disease of Mushroom Workers. Farmer's Lung**

L. S. BRINGHURST, R. N. BRYNE, and J. GERSHON-COHEN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 171, 15-18, Sept. 5, 1959. 2 figs., 9 refs.

The authors describe 16 cases of respiratory disease in mushroom workers seen at Chester County Hospital, Westchester, Pennsylvania, the patients being migrant Puerto Ricans. Symptoms occurred after the bedding-down and cleaning out of damp compost beds containing mouldy hay and silage. The onset was acute, usually within a few hours of starting the work, and the attacks lasted from 4 to 46 days, average 22 days; in 2 patients symptoms lasted 6 months. Symptoms included cough with yellow or greenish sputum and occasionally haemoptysis, pain in the chest, shortness of breath, chill, headache, nausea and vomiting, loss of appetite, loss of weight, sore throat, night sweats, and diarrhoea. The principal signs were fever, temperature often reaching 104° F. (40° C.), tachycardia, and scattered râles throughout both lungs. Polymorphonuclear leucocytosis was present in all cases. Radiologically the lungs showed scattered diffuse infiltration which often became confluent. Resolution was rapid in the acute stage, but in some cases the disease became chronic with increased fibrosis. Bronchiectasis occurred in one patient. [The bacteriology of the sputum is not described.]

The authors state that nitrous fumes are encountered in the process of composting as in recently filled silos; further, the clinical and radiological findings in the cases described are similar to those in farmer's lung and, in many respects, like those in silo-filler's disease. They consider that nitrogen dioxide may be the initiating factor but admit the possibility that mouldy organic dust may be the cause. Kenneth M. A. Perry

1050. **Environmental Exposure to Uranium Compounds: Air, Urine, and Medical Findings**

M. LIPPMANN. *A.M.A. Archives of Industrial Health* [A.M.A. Arch. industr. Hlth] 20, 211-226, Sept., 1959. 11 figs., 13 refs.

Air and urine data and medical findings covering a two-year period are presented for employees of two plants of a uranium refinery. The Plant 1 personnel were exposed to "insoluble" uranium compounds, the Plant 2 personnel to "soluble" uranium.

Monthly average air dust exposures to "soluble" uranium compounds were as high as 3,500 µg. per cubic meter. For 29 men exposed at this level, the median before-weekend urine sample was 900 µg. per litre;

25% exceeded 2,000 μg . per litre, and the highest sample was 13,200 μg . per litre. None of these men showed any diminution of renal function, but 3 of the 29 had abnormal urine findings. For men exposed to lower air concentrations, there were no clinical symptoms and only occasional urine abnormalities.

Monthly average air dust concentrations of "insoluble" uranium compounds were as high as 9,700 μg . per cubic meter. Although respirators were worn at some operations, they could not have reduced average exposures by more than 75%, so that some exposures were in the milligram per cubic meter range. For eight men so exposed, 8 of 33 after-weekend urine samples exceeded 67 μg . per litre, with the highest sample 108 μg . per litre. For men who worked in average air concentrations up to 4,400 μg . per cubic meter only one urine sample in 118 exceeded 67 μg . per litre.

Uranium urine excretion rate after heavy exposures was found to drop steadily for several weeks, and the rate of excretion at any subsequent time is a function of time and the excretion rate during the first day after exposure.

No useful correlation could be found between air concentration of "soluble" uranium compounds and before-weekend urine concentration or between air concentration of "insoluble" uranium compounds and after-weekend urine concentration. In addition, it is shown that an after-weekend urine sample does not provide an accurate indication of uranium body burden. —[Author's summary.]

1051. Spinal Lesions Due to Working with Pneumatic Tools. (Beitrag zur spinalen Schädigung durch Pressluftwerkzeugarbeit)

S. NOVOTNÝ and G. UHER. *Archiv für Gewerbepathologie und Gewerbehygiene* [Arch. Gewerbepath. Gewerbehyg.] 17, 339–346, 1959. 2 figs., 14 refs.

Previous observations on the effects of work with pneumatic tools have been concentrated on the aspect of vasomotor injury to the joints and peripheral nerves; an effect on the spine and central nervous system has rarely been noted. The present authors refer to some cases of this type which have been reported, and describe 2 observed by themselves. They claim that it is possible to distinguish two different forms of this disorder.

In the first case, in a miner, the initial symptom was extreme fatigue in both shoulder joints, spreading later to the lower extremities. The hand muscles showed atrophy, loss of movement, and fibrillary twitching. This was considered to be a case of progressive spinal muscular atrophy or amyotrophic lateral sclerosis due to chronic trauma.

The second patient, a left-handed mason, had for the past 10 years used a pneumatic tool with his left hand. His first symptom was fatigue and amyotrophy of the left hand, with diminished sensation of heat and touch, but increased sensitivity to cold. Transference of the tool to the right hand was followed by similar symptoms in that hand, and the weakness spread to the feet, with loss of the knee and ankle jerks, hypoaesthesia to touch, pain, and cold, and anaesthesia to heat. Radiography

showed progressive spondylarthritis and the man died 4 years later from sudden heart failure. Histological examination showed extensive degenerative changes in the ganglion cells of the brain, medulla, spinal cord, peripheral nerves, and muscles. These were considered to be due primarily to the constant stream of vasomotor impulses from the fingers to the medulla and finally to the whole central nervous system, causing general myelomalacia.

Ethel Browning

1052. The Practicability of Prophylaxis against Lead Poisoning with Sodium Calciumedetate. (Ist die Prophylaxe der Bleikrankheit mit Ca-EDTA möglich?)

R. POTT. *Archiv für Gewerbepathologie und Gewerbehygiene* [Arch. Gewerbepath. Gewerbehyg.] 17, 354–364, 1959. 3 figs., 24 refs.

In a copper-lead refinery employing 2,500 workers, about 600 employees working in specially hazardous conditions have been kept under regular clinical and haematological supervision from 1953 to 1958. Although there has been only one case of severe poisoning (in 1953), slight disturbances of health have caused absenteeism, and any worker with a degree of punctate basophilia exceeding 8 punctate cells in 50 fields, significant porphyrinuria, or both has been considered a "lead carrier".

From 1957 sodium calciumedetate (CaEDTA) has been given by mouth in doses of 3 g. daily for 4 weeks to all workers with more than 20 punctate cells in 50 fields and marked porphyrinuria without interruption of their usual exposure. Estimations of porphyrinuria, punctate basophilia, haemoglobin and blood lead levels, and in some cases urinary lead excretion have been carried out before and after the treatment. The urinary lead excretion in 15 out of 35 cases increased during the first 6 days to about 4 mg. daily, decreasing later. During this time continued exposure was well tolerated, with a diminution of gastro-intestinal disturbance. It is claimed that owing to the more favourable proportion between the possible and actual urinary excretion of lead the oral administration of CaEDTA carries less risk of excessive mobilization of lead from bone depots than intravenous administration.

In the 7 months following the institution of this form of treatment 38 out of 66 workers who had received CaEDTA developed symptoms attributed to lead poisoning, but this may have been due to an unavoidable increase in exposure and it is considered that in these circumstances oral prophylaxis with CaEDTA is worth while. Small doses daily (0.5 to 1 g.) at the beginning of the shift help to bind the lead absorbed with the dust and respiratory mucus and maintain a slightly increased urinary excretion. Such small doses carry no danger of excessive excretion of trace elements and iron. With regard to possible sensitization to CaEDTA and the consequent danger of kidney injury it is advised that careful choice of the individual workers should be made and that they should be kept under constant medical supervision, with frequent estimations of the lead content of the blood and urine and, where possible, of the faeces.

Ethel Browning

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Forensic Medicine and Toxicology

1053. The V-Test. [Monograph, in English]

G. VOLUTER. *Radiologia clinica* [Radiol. clin. (Basel)] 28, Suppl., 1-32, 1959. 7 figs.

Taking as a basis more than 1,000 anthropometric radiographies of the human cranial base, the author proposes the radiological investigation of the sella turcica as a means of identifying disfigured and mutilated victims of accidents due to fire, sea water, and gas or nuclear explosions. The cranial base, covered by the elastic brain mass, itself enclosed as a ball inside the concave cranial bones, is efficiently protected against the worst injuries. As each individual has his specific sella turcica (its distinctive characteristics being shape and volume, angle, varied morphology of the clinoid apophyses, sphenoidal sinus, etc.) the radiological picture serves as a complete anthropometric identification test.

The plan is to identify a victim by comparing an *in-vivo* x-ray of the cranial base with one made on the cadaver. By this means all persons risking damage and mutilation due to conflagration, submersion (air force, army, navy), those exposed to atomic explosion, or fire, railway and aeroplane accidents or who exercise a dangerous profession (miners, sea divers, etc.) could be identified by this method. The technique is simple and rapid. A photoradiographic apparatus utilizing small films may be used at minimal expense.

The author recommends the establishment of radio-anthropomorphic files for army, navy, air force, and police, as well as for insurance companies, industries, etc.—[Author's summary.]

1054. The Elimination of CO in the Urine in Carbon Monoxide Poisoning. (L'eliminazione urinaria del CO nell'intossicazione ossicarbonica)

L. PECORA, S. FATI, and C. VECCHIONE. *Folia medica* [Folia med. (Napoli)] 42, 975-984, Aug. [received Oct.], 1959. 2 figs., 6 refs.

Having previously shown (*Folia med. (Napoli)*, 1957, 40, 482) that carbon monoxide poisoning is not simply due to carboxyhaemoglobin formation, the authors, working at the Institute of Industrial Medicine of the University of Naples, found that in human chronic CO poisoning and in experiments on rabbits the blood iron level was invariably increased, and that in acute CO poisoning in rabbits the administration of iron had a detoxicating effect. They then carried out tests on the following groups of subjects: (1) 6 normal persons with a maximum blood CO level of 0.6 ml.%; (2) 6 persons with a blood CO content of about 1 ml.%; (3) normal rabbits; (4) rabbits with acute CO poisoning; and (5) rabbits with chronic CO poisoning (120 days' exposure). The CO content of the blood and urine, blood and urinary iron content, free erythrocytic protoporphyrin content, and urinary coprophyrin content were determined before and 4 hours after the intravenous injection of

500 µg. of iron per kg. body weight in the rabbits and of 100 mg. of iron saccharate in the human subjects.

In Group 1 the initial urine specimens contained only traces of iron and no detectable CO. After the administration of iron, however, there was an increase in both blood and urinary iron content. In Group 2 before treatment the urinary iron content was increased and CO was present in small quantities, while the blood iron, CO, and protoporphyrin and urinary coproporphyrin levels were elevated. After treatment the blood CO level increased by about 50% and the urinary CO content was at least doubled and in some cases quadrupled. Both blood and urinary iron levels were increased, but there was no change in the porphyrin levels. In Group 4 after treatment the blood CO content increased rapidly, even to 15 or 20 times the initial level, and a very considerable amount of CO was found in the urine, from which it was absent in normal rabbits. In the rabbits of Group 5 the initial blood iron and CO levels were slightly increased, though both were absent from the urine. After the administration of iron the urinary CO content was markedly increased and there was a proportional increase in the blood and urinary iron levels.

The authors conclude that in CO poisoning there is an increase not only in the iron content of the blood, but also in that of the urine. They postulate that CO is eliminated through the urine as well as through respiration and that iron acts as a special vehicle in this process. They consider that in acute and even in chronic CO poisoning the administration of iron is of value in causing a more rapid elimination of CO. W. K. Dunscombe

1055. Parathion Poisoning: Increasing Frequency in Finland

T. TOIVONEN, K. OHELA, and W. J. KAIPAINEN. *Lancet* [Lancet] 2, 175-176, Aug. 22, 1959. 1 fig., 6 refs.

In Finland between 1952 and 1957 there were 286 deaths from parathion pesticides used in agriculture and horticulture. In 1957 the number had risen to 105. Of the total deaths 237 were by suicide. Only 20% of these cases had an opportunity of procuring the poison for their work. The sale of parathion preparations should be more strictly controlled.—[Authors' summary.]

1056. The Treatment of Poisoning during the Past Twenty-five Years. A Retrospective Review

C. CLEMMESSEN. *Danish Medical Bulletin* [Dan. med. Bull.] 6, 209-213, Oct., 1959. Bibliography.

1057. Toxicology of Diisocyanates

R. H. WILSON and G. L. WILSON. *Journal of Occupational Medicine* [J. occup. Med.] 1, 448-450, Aug., 1959. 8 refs.

Anaesthetics

1058. Disinfection in Anaesthesia

H. BEEUWKES and A. E. D. VAN DER VIJVER. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 31, 363-366, Aug. [received Oct.], 1959. 7 refs.

The authors emphasize the importance of adequate sterilization of anaesthetic apparatus, pointing out that the bacterial count of washings from equipment presents the same picture as that of oral flora, the greatest concentration of organisms being observed in the parts proximal to the patient. Since neither tap-water nor a detergent containing 3% hexachlorophane was fully effective, the authors, at St. Joseph Hospital, Heerlen, Netherlands, tried chlorhexidine. Details of the techniques used for disinfecting various parts of the equipment are given. Rubber articles are first cleaned under running tap-water with a synthetic detergent and a culture tube cleaner; after immersion in a solution of 0.1% w/v of chlorhexidine and 0.02% w/v of "tween 80" in distilled water for 30 minutes they are rinsed with saline and dried with sterile compresses. Corrugated rubber equipment is boiled in water for 10 minutes once a week; this is stated to maintain antistatic efficiency. Metal instruments are cleaned mechanically after use and then rubbed over once with 0.1% w/v chlorhexidine in 70% ethyl alcohol applied by cotton wool swabs. Certain special provisions for specific contaminations are also described.

[Although some details of the procedure recommended may not find universal approval, the authors have done a valuable service in drawing attention to this neglected subject.]

Michael Kerr

1059. The Evaluation of Premedication in Children

A. G. DOUGHTY. *Proceedings of the Royal Society of Medicine* [Proc. roy. Soc. Med.] 52, 823-833, Oct., 1959. 16 refs.

In this paper the author discusses means of evaluating methods of preoperative sedation in children and reports his results, based on a trial carried out at Surbiton Hospital, Kingston, Surrey, on 318 children ranging in age from 2 to 12 years, most of whom were undergoing adeno-tonsillectomy under thiopentone and suxamethonium anaesthesia, maintained with nitrous oxide and oxygen and a trace of either halothane, trichloroethylene, or ether. For premedication the patients were divided at random into three equal groups, which received respectively: (1) atropine only, and served as a control group; (2) papaveretum and hyoscine; and (3) methylpentynol and hyoscine; in Groups 1 and 2 the premedication was given subcutaneously into the back of the hand and in Group 3 orally, and at 30, 90, and 90 minutes respectively before operation. The behaviour of the child, who was told beforehand that he would be given an injection, was observed before and during the injection by an observer who was unaware of the type of premedication given. The child's demeanour in the

anaesthetic room was classified as sleepy, cheerful, serious, apprehensive, tearful, or noisy.

The highest proportion of tearful children occurred in Group 1 (atropine only). A high proportion (47 out of 106) of those given methylpentynol and hyoscine were cheerful compared with 24 out of the 106 given papaveretum and hyoscine; also in the latter group 28 out of 106 were apprehensive compared with only 11 out of 106 in Group 3. The response to venepuncture was also observed and shown to be only just significantly better in Groups 2 and 3 than in Group 1. As judged by the single factor of whether the child withdrew his hand or not when venepuncture for anaesthesia was about to be performed methylpentynol and hyoscine was the best form of premedication. When the many detailed results, presented in 14 tables, were divided into the two large groups "satisfactory" and "unsatisfactory" the greatest number of satisfactory results were obtained in the patients given methylpentynol and hyoscine as premedication.

The mean ages of the 3 groups of children were similar, and those over 7 years of age were not better behaved than those under this age. Previous exposure to psychic trauma did not affect the behaviour of the children. Papaveretum and hyoscine caused a significantly greater number of cases of apnoea or hypopnoea at the end of the operation than the other combinations, but respiration returned quickly. No great difference in the number of patients who vomited in the three groups was noted. It is concluded that methylpentynol and hyoscine provide satisfactory premedication, and that there is little advantage in using papaveretum and hyoscine rather than atropine alone.

M. Woods

1060. Upper Airway Obstruction in the Unconscious Patient

P. SAFAR, L. A. ESCARRAGA, and F. CHANG. *Journal of Applied Physiology* [J. appl. Physiol.] 14, 760-764, Sept., 1959. 4 figs., 10 refs.

Airway patency was studied in 80 anesthetized, spontaneously breathing patients, who received no muscle relaxants. With the neck flexed (chin towards chest) the airway was obstructed in all patients, both in the supine and prone positions, with and without an artificial oropharyngeal airway in place. With extension at the atlanto-occipital joint (chin up) in the supine position approximately 50% of the patients had an open airway. The other 50% required, in addition to extension of the neck, forward displacement of the mandible or the insertion of an oropharyngeal airway or both. Roentgenograms demonstrated that the tongue is pushed against the posterior pharyngeal wall when the neck is flexed and the mandible is not held forward. The incidence and degree of obstruction was similar in the prone and supine positions, with comparable positions of the head, neck and mandible.—[Authors' summary.]

Radiology

1061. Roentgenologic Aspects of Cerebral Angiography in Children

J. M. TAVERAS and C. M. POSER. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 82, 371-391, Sept., 1959. 20 figs., 19 refs.

The radiological aspects of cerebral angiography performed 207 times on 138 patients under 13 years of age are presented in this paper from the Presbyterian Hospital (Columbia University), New York. In the majority of these cases percutaneous puncture was employed and 10 serial films exposed, both in the antero-posterior and lateral projections. The main indications for angiography in the series were suspected intracranial aneurysm or vascular malformation, a suspected supratentorial space-occupying lesion, or vascular occlusion.

Cross-filling of the contralateral anterior cerebral artery or even of the middle cerebral artery was not uncommon, even without carotid compression. Filling of the ipsilateral posterior cerebral artery was also encountered in a large percentage of cases; it is suggested that these findings may be related to the lower blood pressure present in children, since the injections were made with approximately the same force as in adults. An important observation was that the middle cerebral artery is situated relatively higher in children than in adults, its site being indicated by a line joining the anterior clinoid processes to a point 2 cm. above the lambda. It was further noted that these arteries descend with advancing age, gradually attaining the adult position.

Analysis of the results in 132 of the cases revealed only normal appearances in 59 cases, but in 58 others the procedure was considered to have helped to elucidate the clinical problem. The lesions found were basically similar to those discovered in adults, but the proportions of types of lesion differed widely, vascular malformations and subdural haematoma being found as frequently as tumours, while only 2 cases of saccular aneurysm were discovered. Other lesions included cerebral atrophy, hemiatrophy, arterial thrombosis, and hydrocephalus.

Arnold Appleby

1062. Roentgenologic Manifestations of Glioma of the Optic Nerve and Chiasm

C. B. HOLMAN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 82, 462-471, Sept., 1959. 12 figs., 25 refs.

From the Mayo Clinic comes this study of the radiological changes observed in 48 patients who proved to have glioma of the optic nerve or chiasma. In 13 of them the tumour involved the optic nerve alone and the views of the optic foramina obtained in 9 of these revealed gross enlargement of one or other optic foramen in 7 cases, while the tumour was shown to be entirely intra-

orbital in the remaining 2. Antero-posterior, Towne's, and stereoscopic lateral radiographs of the whole skull in 12 of the 13 cases had been interpreted as normal. In the other 35 patients the glioma involved the optic chiasm as well as one or in some cases both optic nerves; in only 4 of these cases had the skull survey views been considered normal. The majority of these patients showed changes in the region of the sella turcica, and 16 had some degree of upward concavity of the sphenoid bone between the pituitary fossa and the planum sphenoidale, this change often involving one of the anterior clinoids. Other changes included enlargement of the sella turcica, shortening of the dorsum sellae, and diastasis of the major cranial sutures. Radiographs of the optic foramina were obtained in 12 cases and showed enlargement of one foramen in 4 cases and of both foramina in 8. Of the 48 patients, 43 showed some change on plain films, but only 9 of them underwent any form of contrast examination (pneumoencephalography in 3 cases, ventriculography in 4, and carotid angiography in 2).

The significance of the upward convexity of the sphenoid anterior to the tuberculum sellae, which produces the so-called J-shaped sella, is difficult to assess because it may occur in such diverse conditions as mongolism, neurofibromatosis, cholesteatoma, and even in healthy subjects. Since this configuration approximates to the infantile type of sphenoid rather than the adult it is suggested that the presence of a slowly growing tumour early in life may influence the development of the sphenoid bone to accommodate the mass. It is concluded, however, that glioma of the optic nerve or of the chiasma is nearly always accompanied by changes on plain radiographs and that the finding of enlargement of the optic foramen together with a J-shaped sella is highly suggestive of such a tumour.

Arnold Appleby

1063. Bronchography without Oil and Iodine: the Use of Barium as a Contrast Medium

J. TEIXEIRA and L. C. V. TEIXEIRA. *Diseases of the Chest* [Dis. Chest] 36, 256-264, Sept., 1959. 4 figs., 12 refs.

The iodized oils commonly used for bronchography have certain disadvantages. Their viscosity is such that they readily fill the alveoli and obscure the bronchial tree, and the oil tends to remain in the alveoli for months or years making it difficult later to assess the pulmonary condition radiologically. Furthermore, the oil is not harmless to the pulmonary tissue, and it has been shown that so-called "oil granulomata" resulting from the irritant nature of the medium develop in a proportion of cases.

The more recent use of water-soluble media has not, in the authors' view, been wholly successful, chiefly because the hypertonic nature of the solution causes irritation of the tracheo-bronchial mucosa with resultant

coughing and spasm. The radiograph also lacks the density which is associated with the use of the opaque oil. The great advantage of the water-soluble medium is the rapidity with which the material is eliminated from the lungs. At the Hospital Sanatório Santa Maria, Rio de Janeiro, a suspension of finely divided barium sulphate in water, with methylcellulose as a viscosing and suspending agent, has recently been tried. The preparation, known as "celobar", contains 150 g. of barium sulphate and 2 g. of methylcellulose, and for bronchography 20 g. of celobar is suspended in 30 ml. of physiological saline solution.

This medium is introduced in the normal manner through an intratracheal catheter, excellent delineation of the bronchial tree being obtained. The medium tends to coat the mucosal wall rather than fill the bronchus, and detail in the bronchial tree is observed as far as the fine peripheral branches. After examination the patient is instructed to cough up as much of the material as possible and the residues of barium rapidly disappear, by ciliary action, in a few days. This medium has been used for bronchographic examination in over 200 cases with excellent results; there was no evidence of toxicity. The authors state that the medium is much cheaper than iodized oil and similar preparations.

A. M. Rackow

1064. Attempted Treatment of Acute Leukaemia in Remission by Whole-body Irradiation followed by Transfusion of Homologous Bone Marrow. (Essai de traitement de sujets atteints de leucémie aiguë en rémission par irradiation totale suivie de transfusion de moelle osseuse homologue)

G. MATHÉ, J. BERNARD, L. SCHWARZENBERG, M. J. LARRIEU, C. M. LALANNE, A. DUTREIX, P. F. DENOIX, J. SURMONT, V. SCHWARZMANN, and B. CÉOARA. *Revue française d'études cliniques et biologiques* [Rev. franç. Ét. clin. biol.] 4, 675-704, Sept., 1959. 20 figs., bibliography.

In three patients with acute lymphoblastic leukaemia in remission, total body radiation with ^{60}Co with a dosage of about 850 rads was given followed by transfusion of homologous marrow.

The clinical and biological sequelae can be grouped into several phases. (a) During the first week, digestive disturbances and a lymphoid and myeloid pancytopenia were present. (b) Total aplasia persisted for the next 10 to 15 days. At first with little clinical disturbance, but later fever, necroses and a haemorrhagic tendency occurred. One of the patients died with a respiratory complication before any evidence of marrow activity had returned. (c) In the other patients, the cytopenia gradually diminished between the 18th and 28th days after irradiation. The clinical symptoms disappeared from the time of the reappearance of circulating granulocytes. (d) Between the 28th and 40th days the clinical and haematological picture was satisfactory. (e) About the 45th day, a "secondary syndrome" developed, with digestive symptoms, infections, loss of weight, abnormal γ globulins and lymphoid aplasia. This syndrome disappeared a month later when the lymphocyte count rose at the same time as the red cells of the donor phenotype

disappeared; the latter had remained at a plateau during the previous 3 months.

A relapse of the leukaemia occurred in the 2 patients after 6 and 5 months of complete remission.—[From the authors' summary.]

1065. Supervoltage (2-Mvp) Rotation Irradiation of Cancer of the Bladder

M. FRIEDMAN. *Radiology* [Radiology] 73, 191-208, Aug., 1959. 20 figs., 12 refs.

This preliminary report from the Hospital for Joint Diseases and New York University College of Medicine, New York, concerns the treatment of cancer of the bladder by means of 2-million-volt x-rays using a rotation technique. The results obtained are discussed. The author considers that for the destruction of the majority of bladder cancers doses ranging from 8,000 to 10,000 rads in a period of 40 to 60 days are required. These high doses require well-collimated supervoltage x-rays and a rotation technique employing a high degree of accuracy in beam-direction. By these means the volume irradiated is kept small and the doses required actually achieved. The beam-direction method employed by the author is described in detail. All patients are treated standing erect and rotated through 360°, the tube remaining stationary.

Using this technique he has treated, either radically or palliatively, 81 cases of bladder cancer from June, 1951, to June, 1958. Of these, 60 (75%) were cases of recurrent growth after surgical treatment, while 21 (25%) presented as untreated. Classification according to the histological grade as well as the clinical stage of the disease, using the Marshall scatter diagram, disclosed remarkably few cases of early lesions. Altogether there were 13 survivors out of 58 treated (22%) after 3 years and 4 out of 31 (13%) after 5 years. The survival rate at 3 years for previously untreated tumours was 42% (5 out of 12) and for recurrent tumours 18% (6 out of 33). [The discrepancies in these figures are not explained.—EDITOR.] It is suggested that the results can be improved if repeated surgical procedures are discontinued in inappropriate cases and radiotherapy instituted at an earlier stage. Previous surgical intervention was considered to be responsible for the severity of the irradiation cystitis observed.

From a brief comparison of the results of different methods of treating bladder cancer the author concludes that those of supervoltage rotation therapy are probably slightly better than those of radical surgery, but that treatment by means of a central intracavitary source (Friedman and Lewis, *Amer. J. Roentgenol.*, 1958, 79, 6; *Abstr. Wld Med.*, 1958, 24, 80) is superior to both other methods in his experience. W. Constable

1066. Sarcoma: Incidence and Results of Treatment. A Study Based on 568 Histologically Verified Cases Seen at the Central Institute of Radiotherapy in Helsinki. [Monograph, in English]

M. ROUKKULA. *Annales chirurgiae et gynaecologiae Fenniae* [Ann. Chir. Gynaec. Fenn.] 48, Suppl. 91, 1-171, 1959. 54 figs., bibliography.